Antibiotics and antiseptics to prevent infection in cardiac rhythm management device implantation surgery

Review information

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Abstract

Background

Surgical site infections (SSIs) resulting from cardiac rhythm management device (CRMD) implantation cause significant morbidity and mortality worldwide, and appear to be increasing at a disproportionately higher rate than the actual rate of CRMD implantation. The prophylactic administration of antibiotics and antiseptics may reduce this infection rate.

Objectives

To determine whether the prophylactic administration of antibiotics and antiseptics in patients undergoing CRMD implantation reduces the incidence of SSI.

Search strategy

We searched the Cochrane Wounds Group Specialised Register (searched 13 April 2011); the Cochrane Central Register of Controlled Trials (CENTRAL) (The Cochrane Library 2011, Issue 2); Ovid MEDLINE (1950 to March Week 5 2011); Ovid MEDLINE (In-Process & Other Non-Indexed Citations, April 11, 2011); Ovid EMBASE (1980 to 2011 Week 14); and EBSCO CINAHL (1982 to 8 April 2011). No date or language restrictions were applied.

Selection criteria

Randomised controlled trials involving any participants receiving either a first-time, or replacement, CRMD implant, comparing any perioperative regimen of antibiotic and antiseptic prophylaxis, with post-procedure infection as a primary outcome measure.

Data collection and analysis

Two review authors independently screened papers for inclusion, assessed risk of bias, and extracted data using a data collection form. Data were pooled where appropriate.

Main results

Fifteen studies (3970 participants) were included in this review. For patients undergoing a CRMD implant, perioperative systemic antibiotics (PSA) delivered approximately one hour prior to the procedure significantly reduced the incidence of SSI compared with no antibiotics (risk ratio (RR) 0.13; 95% CI 0.05 to 0.36; P value < 0.00001). Furthermore, PSA plus antiseptics delivered as above significantly reduced the incidence of postoperative infection when compared with antibiotics delivered postoperatively (RR 0.14; 95% CI 0.03 to 0.60; P value 0.008).

Authors' conclusions

The evidence suggest that antibiotic prophylaxis within one hour prior to CRMD implantation is effective at reducing SSI. These findings should be interpreted with caution, however, as the quality of the evidence assessed was poor.

Plain language summary

Routine use of antibiotics and antiseptics around the time of surgery reduces risk of infection after pacemaker surgery

A pacemaker (also called "cardiac rhythm management devices" or CRMD) is inserted during a surgical procedure and infections sometimes occur after insertion which can be life threatening. Antibiotics are routinely used to prevent infection in people having surgery with the aim of reducing the number of infections. This review is concerned with people having pacemakers implanted surgically and aimed to assess the evidence for the routine use of antibiotics to reduce infection. The review found that antibiotics delivered intravenously up to one hour before the surgical procedure are effective in reducing the number of postoperative infections.

Background

Description of the condition

Worldwide there are millions of people with functioning cardiac rhythm management devices (CRMDs), including pacemakers and implantable cardioverter defibrillators (ICDs). Furthermore, hundreds of thousands of these devices are implanted each year (Ector 2007; Kurtz 2010). Many of these CRMDs are implanted in elderly people and people with co-morbidities that predispose them to infection. The incidence of surgical site infection after implantation of these devices ranges from 0.13% to 19.9%; this particular complication is associated with substantial morbidity, mortality and financial cost (Baddour 2003; Hill 1987; Lai 1998; Mela 2001; Smith 1998). In addition, two different, large databases in the US have reported a disproportionate rise in CRMD infections relative to the rate of new CRMD implantation (Cabell 2004; Voigt 2006). While it is not entirely clear why this acceleration in the infection rate has occurred, it has been suggested by both Cabell 2004 and Voigt 2006 that this may reflect the growth in ICD use, and; that an improved understanding of the presentation (e.g. better means of identification and tracking of infection), and management of cardiac device infections may also have identified SSI that were heretofore not able to be identified . Furthermore, many patients present with co-morbidities that may compromise their immune systems. Voigt 2006 further suggests that the acceleration may reflect an increase in the proportion of ICDs implanted by less experienced personnel, or in smaller centres (operator volume appears to be inversely linked to higher rates of complications and infections - i.e. complication rates [including infection] rise as operator volume decreases).

In general, mortality attributable to infections associated with surgical implants is highest among patients with cardiovascular implants, including CRMDs. This mortality is due to the co-morbidities associated with these patients (e.g. congestive heart failure, conduction abnormalities, paravalvular abscesses, valve dehiscence, and serious peripheral embolisation). Additionally, because of these co-morbidities, some patients must be treated medically not surgically. Medical treatment alone, may result in recurrence of endocarditis, which warrants surgery, and carries a high mortality (Darouiche 2004). Infections associated with CRMDs incur significant treatment costs. Published literature indicates the treatment costs can be as high as USD 83,000 per implant (Chu 2005). Using an average infection rate of 5.3%, costs for treating these types of infections would exceed USD 3.8 billion in the US alone (870,000 implants x 0.053 x USD 83,000) (Voigt 2006).

Several countries, including the USA and UK, have implemented measures to promote the practice of administering systemic prophylactic antibiotics for the prevention of surgical site infections (Bratzler 2004; SIGN 2010). Guidelines and evidence grading of the duration and timing of systemic antibiotic prophylaxis have been developed by various medical specialties for other types of surgical procedures (Edwards 2006; Engelman 2007; Fletcher 2007; O'Grady 2002). Some independent organisations that establish national guidelines for promoting good health and preventing and treating poor health (i.e. National Institute for Health and Clinical Excellence (NICE) in the UK; the Scottish Intercollegiate Guidelines Network (SIGN); and the American Heart Association (AHA); (Baddour 2010)), have recently issued recommendations regarding the use of antibiotic prophylaxis for CRMDs. Some provider institutions in the UK have even made specific recommendations (within protocols) regarding which types of antibiotics should be used perioperatively. These practices, however, have not yet become widespread in the medical community. For example, in a review of a major medical association's practice guidelines for device-based therapy of cardiac rhythm abnormalities, there is no mention of the use or need for systemic antibiotic prophylaxis during CRMD implantation (Epstein 2008). Some clinicians have recognised the need to develop definitive guidelines to prevent CRMD infections, as there is little, or no, standardised use of systemic prophylactic antibiotics when

implanting CRMDs (Movahed 2004). It has been noted in peer-reviewed journals that antibiotic prophylaxis for nonvalvular cardiovascular devices is modelled after that used to prevent surgical site infection (Baddour 2003). Yet due to differences in the pathogenesis of device-based versus non-device-based infection and variations among different types of surgical implants (in terms of the microbiology of infection and the period of time it takes for indwelling implants to become covered with endothelial or fibrotic tissue), the clinical efficacy of a "generic" antibiotic prophylactic approach may not apply to all implants (Darouiche 2003).

Implanted devices harbour various micro-organisms within a layer of biofilm (a thin, resistant layer of micro-organisms, such as bacteria) that coats the device (Donlan 2002). Biofilms develop on more than 25% of devices implanted during hospitalisation (Hazan 2006). These biofilm-embedded pathogens are more resistant to conventional antibiotic agents than their planktonic counterparts (i.e. micro-organisms floating and drifting within the circulatory system) (Gilbert 2003). Bacteria form biofilms as a basic survival strategy in the many environments in which they proliferate (Donlan 2002). The biofilm structure protects the bacteria from antibacterial chemicals (including natural antibiotics), environmental bacteriophages (viruses that can infect or kill a bacterium), and phagocytic amoebae (amoebae that engulf a bacterium and kill it). Biofilms help protect bacteria from their natural, and unnatural, predators. Bacteria preferentially form a biofilm in very high shear environments (i.e. rapidly flowing surroundings, such as blood flow), and these can form as easily on smooth surfaces as on rough. In a biofilm, bacteria become encased in a polysaccharide matrix (carbohydrates joined by glycosidic bonds), which prevents predators from attacking the bacteria residing within or under it. Bacteria encased in these biofilms can be up to 1000 times more resistant to antimicrobial stress than free-swimming planktonic bacteria of the same species (Parsek 2003; Wolcott 2008). Furthermore, biofilms permit the bacteria embedded within them to remain inactive on the surface of the implant for years before clinical presentation (Fishman 1997). This issue of latent infection is demonstrated by the observation that more than 75% of CRMD implant-related infections occur after hospital discharge (i.e. more than 30 days after the surgical procedure) (Chua 2000). It is therefore important to consider the impact that biofilm formation plays when determining the antibiotics that may be effective in preventing infection.

There are other risk factors that correlate with rates of infection in implanted CRMDs both positively (increasing the risk) and negatively (decreasing the risk). Positively-correlated risk factors include: fever 24 hours before the procedure; use of temporary pacing before CRMD implantation (temporary pacing [the insertion of a temporary pacemaker] is sometimes required during permanent pacemaker implantation; based on the patient's condition); and early re-interventions. Negatively-correlated risk factors include: implantation of a new system and antibiotic prophylaxis (use of antibiotics prior to the procedure to prevent infection) (Klug 2007).

The definition of a surgical site infection with an implant as defined by the Centers for Disease Control (CDC) is as follows (Horan 2008):

- Infection occurs within one year if implant is in place and the infection appears to be related to the operative procedure *and;*
- Involves deep soft tissue of the incision *and;*
- Patient has at least one of the following:
  - purulent drainage from the deep incision but not from the organ/space component of the surgical site;
  - a deep incision spontaneously dehisces or is deliberately opened by a surgeon and is culture positive or not cultured when the patient has at least *1* of the following signs or symptoms: fever (>38^{o} C), or localized pain or tenderness. A culture-negative finding does not meet this criterion.
  - an abscess or other evidence of infection involving the deep incision is found on direct examination, during reoperation, or by histopathologic or radiologic examination.
  - diagnosis of a deep incisional SSI by a surgeon or attending physician.

Description of the intervention

Protocols and guidelines that address antibiotic and antiseptic prophylaxis have been developed for various types of surgical procedures, but while recommendations have been published regarding the use of antibiotic prophylaxis (as noted above) there has been a very limited number of specific protocols or guidelines, to date, for CRMD implants. Antibiotic prophylaxis is defined as perioperative (perioperative - care that is given just before, during and after surgery) administration of antibiotics (commonly administered systemically via intravenous catheter or intravenously (IV)) or orally for preventing postoperative SSIs commonly caused by pathogens that reside on the patients' skin. (Although antibiotics can be administered locally - i.e. during the procedure into the wound site). Antiseptic prophylaxis is defined as preoperative cleansing or scrubbing of the patients' skin around the surgical site in order to prevent surgical-site infection. Antiseptic prophylaxis is administered commonly in surgical procedures and includes chlorhexidine alcohol or povidone iodine (Darouiche 2010) General surgical guidelines generally support antibiotic administration within one hour prior to initiation of the surgical procedure (perioperative period), with discontinuation 24 to 48 hours post procedure (Bratzler 2004). The types of antibiotics administered include: cefazolin, vancomycin, cefepime, aztreonam, ciprofloxacin, levofloxacin, trimethoprim/sulfamethoxazole, and linezolid. Antiseptics in routine use include chlorhexidine, povidone-iodine, and alcohol (applied via an applicator in a "scrubbing" manner). It is therefore important to take into consideration the variations between antibiotics (type, how, when, and where they are administered) with regard to their ability to prevent SSIs after CRMD implantation. It is also important to take into consideration they type of antiseptic used in the CRMD implant procedure as it has been discovered in a prior randomized controlled trial (RCT) that chlorohexidine-alcohol antiseptics are superior to povidone-iodine (Darouiche 2010) This RCT evaluated the use of antiseptics in colorectal, small intestinal, gastroesophageal, biliary, thoracic, gynecologic, and urologic surgical procedures.

How the intervention might work

When properly administered, prophylactic antibiotics significantly reduce the incidence of surgical infection (Classen 1992). Despite the fact that Classen 1992 studied a population of patients who underwent surgical procedures which did not require device implantation, he demonstrated that antibiotics administered intravenously (systemically) up to one hour prior to the procedure reduced surgery-related infections. Based on the findings of this study, the application and timing of antibiotic prophylaxis appears to have become "standardised" for most types of surgical procedures. Recently, it has also been demonstrated that optimal preoperative skin antisepsis can decrease the incidence of surgical-site infections in the absence of surgical implants significantly (Darouiche 2010). Thus the addition of effective skin antiseptics with proper antibiotic prophylaxis has the potential of further reducing the occurrence of infections associated with surgical implantation of CRMD devices.

Why it is important to do this review

These interventions (prophylactic antibiotics with, or without, antiseptics, or antiseptics alone as well as the timing of antibiotic administration and route of administration delivered - local or systemic) have not been specifically addressed with respect to CRMD implantation. CRMD-related infections cause significant morbidity and mortality, and their treatment costs healthcare systems - worldwide - billions of dollars each year. The proper administration of antibiotic and antiseptic agents may reduce the frequency of these types of infections, and so reduce the overall healthcare expenditure in these patients. A meta-analysis of prospective, randomised trials on antibiotic prophylaxis has supported the role of a definite prophylactic effect of antibiotics when implanting pacemakers (Da Costa 1998), however, this review is now out of date (with the last search date being June 1996), and did not include all prospective randomised trials related to route of administration and timing . There are likely to be new prospective, randomised trials that have addressed a range of issues including: type of antibiotic(s), route of administration, and duration that should be considered. There is continued uncertainty regarding the efficacy, duration, and economics (cost effectiveness) of prophylactic regimens. This uncertainty exists because of the lack of published clinical guidelines or recommendations made by medical associations that implant CRMDs - despite a meta-analysis demonstrating a protective effect of antibiotic prophylaxis (Da Costa 1998) . This review will consider additional information on: whether prophylactic antibiotics plus antiseptics, the route of administration, or the timing of administration reduce the incidence of CRMD-related infections.

Objectives

To determine whether prophylactic (systemic or local) administration of antibiotics and local administration of antiseptics, in combination or separately, in patients undergoing surgical implantation of pacemakers and cardioverter-defibrillators (CRMDs) reduces the incidence of SSIs and other hospital-acquired infections post surgery.

Methods

Criteria for considering studies for this review

Types of studies

Randomised controlled trials (RCTs) that determine the short- and longer-term effect on rates of SSI of antibiotic and antiseptic prophylaxis during CRMD implantation will be eligible for inclusion. Quasi-randomised trials (QRCTs), defined as those trials where participants were randomised via allocation by date of birth, day of the week, medical record number, month of the year, or the order in which participants were included in the study (e.g. alternation), were not considered because suitable RCTs were identified.

Types of participants

Any person undergoing initial, or repeat, implantation of a pacemaker or cardioverter-defibrillator.

Types of interventions

Any regimen of systemic or local antibiotic prophylaxis, singly or in combination,administered at the time of surgical implantation of CRMD. Systemic antibiotic administration is defined as intravenous or oral perioperative antibiotic administration. Local antibiotic administration is defined as intra-operative antibiotic administration at the open surgical site. Eligible comparisons in trials included:

Comparisons:

- Systemic antibiotics plus local antiseptics compared with local antiseptics alone;
- Local or systemic antibiotics compared with no antibiotics or placebo;
- Systemic antibiotics compared with local antibiotics;
- Any antiseptic compared with no antibiotic/no antiseptic or placebo;
- Comparisons of antibiotics administered for different periods of time and/or duration;
- A systemic antibiotic compared with another systemic antibiotic;
- A local antibiotic compared with another antibiotic;
- A local antiseptic compared with another antiseptic

Types of outcome measures

Primary outcomes

- Rates of surgical site infection (including septicaemia, septic shock, infective- or bacterial endocarditis, endocarditis, unspecified valve infection, cellulitis).

- Adverse events.

Secondary outcomes

- Rates of infection of first time CRMD implants versus repeat CRMD implants
- All healthcare costs.

Search methods for identification of studies

Electronic searches

We searched the following electronic databases:

- The Cochrane Wounds Group Specialised Register (searched 13 April 2011);
- The Cochrane Central Register of Controlled Trials (CENTRAL) (The Cochrane Library 2011, Issue 2);
- Ovid MEDLINE (1950 to March Week 5 2011);
- Ovid MEDLINE (In-Process & Other Non-Indexed Citations, April 11, 2011);
- Ovid EMBASE (1980 to 2011 Week 14);
- EBSCO CINAHL (1982 to 8 April 2011).

We searched the Cochrane Central Register of Controlled Trials (CENTRAL) using the following exploded MeSH headings and keywords:

#1 MeSH descriptor Vancomycin explode all trees
#2 MeSH descriptor Cephalosporins explode all trees
#3 MeSH descriptor Ciprofloxacin explode all trees
#4 MeSH descriptor Ofloxacin explode all trees
#5 MeSH descriptor Aztreonam explode all trees
#6 MeSH descriptor Trimethoprim-Sulfamethoxazole Combination explode all trees
#7 MeSH descriptor Oxazolidinones explode all trees
#8 (antibiotic* or antibacterial* or antimicrobial* or cefazolin or cefepime or vancomycin or aztreonam or ciprofloxacin or levaquin or trimethoprim or linezolid):ti,ab,kw
#9 MeSH descriptor Anti-Infective Agents, Local explode all trees
#10 antiseptic*:ti,ab,kw
#11 MeSH descriptor Iodophors explode all trees
#12 MeSH descriptor Chlorhexidine explode all trees
#13 MeSH descriptor Povidone-Iodine explode all trees
#14 MeSH descriptor Alcohols explode all trees
#15 (iodophor* or povidone or iodine or chlorhexidine or betadine or alcohol*):ti,ab,kw
#16 (#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15)
#17 MeSH descriptor Surgical Wound Infection explode all trees
#18 MeSH descriptor Surgical Wound Dehiscence explode all trees
#19 (surg* NEAR/5 infect*):ti,ab,kw
#20 (surg* NEAR/5 wound*):ti,ab,kw
#21 (surg* NEAR/5 site*):ti,ab,kw
#22 (surg* NEAR/5 incision*):ti,ab,kw
#23 ((post-operative or postoperative) NEXT (wound NEXT infection*)):ti,ab,kw
#24 (#17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23)
#25 MeSH descriptor Pacemaker, Artificial explode all trees
#26 MeSH descriptor Defibrillators, Implantable explode all trees
#27 MeSH descriptor Cardiac Pacing, Artificial explode all trees
#28 pacemaker*:ti,ab,kw
#29 (cardioverter NEXT defibrillator*):ti,ab,kw
#30 (implantable NEAR/3 defibrillator*):ti,ab,kw
#31 ((cardiac NEXT rhythm NEXT management NEXT device*) or CRMD*):ti,ab,kw
#32 (#25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31)
#33 (#16 AND #24 AND #32)

The search strategies for Ovid MEDLINE, Ovid EMBASE and EBSCO CINAHL can be found in Appendix 1; Appendix 2 and Appendix 3 respectively. The Ovid MEDLINE search was combined with the Cochrane Highly Sensitive Search Strategy for identifying randomized trials in MEDLINE: sensitivity- and precision-maximizing version (2008 revision) (Lefebvre 2009). The Ovid EMBASE and EBSCO CINAHL searches were combined with the trial filters developed by the Scottish Intercollegiate Guidelines Network (SIGN) (SIGN 2010). There were no restrictions on the basis of date or language of publication.

Searching other resources

We contacted corresponding authors as well as the manufacturers and distributors of linezolid, quinupristin/dalfopristin, daptomycin and other antistaphylococcal (i.e. antibiotic) agents (Pfizer, Cubicin), and antiseptic manufacturers (CareFusion). Further searches were made of US Food and Drug Administration (FDA) briefing documents used in the licensing of antistaphylococcal agents. The citation lists of papers identified by the above strategies were checked for further reports of eligible studies. We undertook handsearches of the following journals:

- *Pacing and Clinical Electrophysiology* (2000 to June Week 4 2010);

- *Circulation: Arrythmia and Electrophysiology* (2008 to June Week 4 2010);
- *Journal American College of Cardiology* (Supplements/abstracts to the Annual American College of Cardiology meeting 2000 to June Week 4 2010);
- *Circulation* (Supplements/abstracts from the scientific sessions 2000 to June week 4 2010);
- *HeartRhythm* (2004 to June Week 4 2010).

Data collection and analysis

Selection of studies

Two review authors screened the titles and abstracts of all studies identified in the search strategy. Full text versions were obtained of all studies identified as potentially relevant, and these were assessed for inclusion by two review authors, using an eligibility pro forma screening document based on pre-specified inclusion and exclusion criteria. Any disagreement between the two review authors was resolved by discussion, or adjudicated by a third party.

Data extraction and management

A data extraction form was developed to aid in the collection of details from included studies. One review author independently extracted the data, and a second review author validated the extracted data. Appendix 5 contains this form. If more than one publication arose from the same study, all versions were considered to maximise data extraction and the primary publication was identified along with the secondary references.

Assessment of risk of bias in included studies

Two review authors independently assessed each included study using the Cochrane Collaboration tool for assessing risk of bias (Higgins 2009). This tool addresses six specific domains, namely sequence generation, allocation concealment, blinding, incomplete outcome data, selective outcome reporting and other issues (e.g. extreme baseline imbalance) (see Appendix 4 for details of criteria on which the judgement was based). Blinding and completeness of outcome data was assessed for each outcome separately. A risk of bias table was completed for each eligible study. Any disagreement amongst review authors was discussed to achieve a consensus.

An assessment of risk of bias using a 'risk of bias summary figure', which presents all of the judgments in a cross-tabulation of study by entry was evaluated. This display of internal validity indicates the weight the reader may give the results of each study. We incorporated the results of the risk of bias assessment into the review through systematic narrative description and commentary about each of the domains, leading to an overall assessment of the risk of bias of included studies and a judgement about the internal validity of the results.

Measures of treatment effect

Each study is reported separately. The results of binary outcomes (i.e. infection or not) are descriptively summarised as percentages, and treatment comparisons presented as risk ratios (RR) with corresponding 95% confidence intervals (CI) . For continuous data, we used the mean difference (MD) where outcomes were measured in the same way between trials. We used the standardised mean difference (SMD) to combine trials that measured the same outcome, but used different methods.

Unit of analysis issues

Where clustering existed, if study comparisons did not account for clustering during analysis, we planned to re-analyse this by calculating an effective sample size where possible. In the unlikely event that the intra-class correlation coefficient (ICC) for clustering had been reported, this was used to estimate the effective sample size. Otherwise, an attempt would have been made to estimate the ICC using external sources. If re-analysed, the P value was annotated as "re-analysed".

If trials included multiple intervention groups (e.g. different antibiotics), we split the shared control group into two or more groups with smaller sample sizes, depending upon the number of interventions, and included 2 or more comparisons.

Dealing with missing data

Missing data for determining percentages were not anticipated for binary primary outcome variables. However, study design characteristics that are needed for subgroup analyses or meta-regression might be missing, and, in such cases, we attempted to contact authors and requested the missing data and information. This was also the case for missing data relating to secondary outcomes such as cost data. If we were unsuccessful in obtaining missing data, we made assumptions about whether the data were missing "at random" or "not at random". In the latter case, we imputed replacement values in order to compare the data by meta-analysis using the average of all observations made after the missing values (post), or the last observation carried forward (LOCF), if no following assessments were made. This would require a sensitivity analysis to assess the impact of the assumptions made.????? We also address the impact of missing data in the discussion. In the case of abstracts we contacted authors to see if a paper had been published in a peer reviewed journal and to ask for clarification on study characteristics and biases.

Assessment of heterogeneity

Assessment of statistical heterogeneity was made using the I^2 statistic in order to determine appropriateness for meta-analysis. If the I^2 statistic was at, or below, 60%, the heterogeneity was considered to be moderate and meta-analysis appropriate. If the value was greater than 60%, sensitivity analysis was undertaken in an attempt to identify which studies were most likely to be causing the problem. If there were only a few such studies, and they could be identified, the reasons for their difference were explored, and the appropriateness of removing these studies was determined. When appropriate,

the meta-analysis was performed with these studies excluded.

Assessment of reporting biases

We used a funnel plot to assess reporting bias. Each primary outcome was reported separately. Furthermore, an assessment was made of publication bias (including a review of unpublished studies); location bias (types of journals) and language bias.

Data synthesis

Where possible we grouped (pooled) similar studies together. In the absence of heterogeneity (I^2 = 0%) or in the presence of low heterogeneity (I^2 statistic less than 40%) a fixed-effect model was used. If heterogeneity was moderate (I^2 statistic greater than 40%, and less than or equal to 60%) a random-effects model was used.

Subgroup analysis and investigation of heterogeneity

If the heterogeneity was too high (greater than 60%), and pooling was not considered relevant, the results were presented as a narrative. However, in no cases where data was pooled was this done at heterogeneity was <60%.

Sensitivity analysis

A sensitivity analysis was performed to determine the effect of study quality on the results. Studies were classified as high quality if allocation was concealed, if bias due to non-blinding was unlikely (blinding of patient/care giver/outcome assessor) , and if incompleteness of outcome data was addressed.

Results

Description of studies

Results of the search

See also: Characteristics of included studies; Characteristics of excluded studies.

We screened 94 records identified via the electronic search, and, of those, 11 were considered to meet the inclusion criteria (Bluhm 1984; Bluhm 1985; Bluhm 1986; De Lalla 1990; De Oliveira 2009; Glieca 1987; Mounsey 1994; Muers 1981 Ramsdale 1984; Ucchino 1982; Walter 1978). Based on handsearches of other journals, and citation reviews of the studies identified via electronic searches another five studies (six citations) were identified (Chaudhry 2005; Dwivedi 2001; Dwivedi 2009; Lüninghake 1993; Martinelli 2006; Morito 2006). Martinelli 2006 was a further citation of the study by De Oliveira 2009 and was considered for data extraction, but cited as a secondary reference. Since suitable RCTs were identified, QRCTs were not considered.

Included studies

The search strategy identified 15 prospective randomised trials in which intravenous antibiotic was compared with no antibiotic, placebo, an alternative antibiotic, an antibiotic delivered by an route of administration, local antibiotic or an alternative antibiotic regimen (e.g., different timing or duration).

Length of follow-up

Length of follow-up for evaluation of infection rate was one week or less in three studies (Glieca 1987; Morito 2006; Walter 1978), but a number had follow-up that exceeded a year (Chaudhry 2005; De Lalla 1990; Lüninghake 1993; Mounsey 1994; Ramsdale 1984). The other studies fell within a range of six to 43 months' follow-up (Bluhm 1984; Bluhm 1985; Bluhm 1986; De Oliveira 2009;Dwivedi 2001). The length of follow-up was unclear for two studies (Dwivedi 2009; Ucchino 1982).

Source of funding and disclosures

Only one study reported disclosures (De Oliveira 2009), of which there were none.

Antibiotics/antiseptics: type, timing, duration, and route

Type of antibiotic used

For perioperative systemic antibiotic (PSA) prophylaxis, there were no dose adjustments for body weight or for length of procedure. All doses were empirically provided. Antibiotics used included: beta-lactum antibiotics: cephalosporins, specifically cephalothin (Walter 1978), cefazolin (Chaudhry 2005; De Oliveira 2009; Glieca 1987; Morito 2006), cefazedone (Lüninghake 1993), cefamandole, cefoxitin, cefotaxime, and cefuroxime (Ucchino 1982); flucloxacillin (Bluhm 1985; Bluhm 1986, Mounsey 1994); cloxacillin (Bluhm 1984; Dwivedi 2001; Ramsdale 1984); and mezlocillin (De Lalla 1990). Some antibiotics were used in combination: netilmicin was provided with mezlocillin (De Lalla 1990), and amoxicillin/ampicillin with cloxacillin (Dwivedi 2001; Ramsdale 1984). Monotherapy also included teicoplanin (Dwivedi 2009); vancomycin (Chaudhry 2005), and oral fluoroquinolones (levofloxacin) (Morito 2006). Antibiotics used for local antibiotic prophylaxis included: rifampicin (Ucchino 1982); combination neomycin, bacitracin, polymyxin B (Ramsdale 1984; cloxacillin (Bluhm 1985) and; gentamicin (Dwivedi 2001).

Timing of antibiotics

In most cases, systemic antibiotics were administered an hour or less before the implantation of the CRMD or the start of the procedure (Bluhm 1984; Bluhm 1985; Bluhm 1986; Chaudhry 2005; De Lalla 1990; De Oliveira 2009; Mounsey 1994; Walter 1978).

In four studies, however, antibiotic prophylaxis was administered outside this window (i.e. more than one hour before the

procedure started). In the Lüninghake 1993 study, systemic antibiotics were administered 90 minutes prior to the procedure. In the Dwivedi 2001 study, cloxacillin prophylaxis was administered IV two hours prior to the procedure, and, in the Morito 2006 study, oral levofloxacin was also administered two hours prior to the procedure. Lastly, in the Dwivedi 2009 study, teicoplanin was administered two hours prior to the procedure.

In the Lüninghake 1993 study, patients with an intercurrent infection were being treated with an antibacterial agent preoperatively (type not noted) and thus did not receive antibiotic prophylaxis perioperatively.

Antibiotic prophylaxis was administered after the procedure in one study (Walter 1978).

Finally, the timing of antibiotic prophylaxis was unclear in two studies (Glieca 1987; Ucchino 1982).

Route of administration of antibiotics

In the majority of studies, antibiotic prophylaxis was administered systemically via IV (Bluhm 1984; Bluhm 1985; Bluhm 1986; Chaudhry 2005; De Lalla 1990; De Oliveira 2009; Dwivedi 2001; Dwivedi 2009; Glieca 1987; Lüninghake 1993; Morito 2006; Mounsey 1994; Ramsdale 1984; Walter 1978).

In two studies, antibiotic prophylaxis was administered both systemically and locally (Dwivedi 2009; Ramsdale 1984). In two studies the route of monotherapy antibiotic prophylaxis administration varied: IV or parenteral versus oral (Morito 2006), or local (Ucchino 1982). In one study (Ucchino 1982), the antibiotic prophylaxis was delivered parenterally (unclear if intramuscularly (IM) or IV).

Duration of antibiotic prophylaxis

The duration of systemic antibiotic prophylaxis varied from immediate cessation post procedure (De Lalla 1990; De Oliveira 2009; Lüninghake 1993); through less than two days (Bluhm 1984; De Lalla 1990; Dwivedi 2001; Dwivedi 2009; Mounsey 1994; Ramsdale 1984; Ucchino 1982; Walter 1978); to a maximum of seven days (Bluhm 1985; Bluhm 1986; Chaudhry 2005 ; Dwivedi 2001; Glieca 1987; Morito 2006).

Antiseptics used perioperatively

Five studies used 0.5% alcoholic chlorhexidine (Bluhm 1984; Bluhm 1985; Bluhm 1986; De Lalla 1990; Mounsey 1994). Two studies used a combination of povidone-iodine plus 0.5% alcoholic chlorhexidine (De Oliveira 2009; Ramsdale 1984). One study used povidone-iodine and a combination of Savlon, ether, and iodine (Dwivedi 2001). The type of local antiseptic used was not reported in five studies. (Chaudhry 2005; Glieca 1987; Lüninghake 1993; Morito 2006; Ucchino 1982).

Excluded studies

The Muers 1981 study was excluded because it was a quasi-randomised trial and this type of study design was not eligible for inclusion since we had identified RCTs (see Characteristics of excluded studies table).

Risk of bias in included studies

Methodological quality of studies was assessed using the Cochrane Handbook for Systematic Reviews on Interventions Version 5.0.2 Risk of Bias guidance (Higgins 2009). Allocation concealment, blinding, blinding of primary outcome, intention-to-treat (ITT) analysis, power calculation, and clear definition of infection were assessed for each study. The quality of most studies was poor to moderate. Only one study was adequately powered to test its hypothesis with confidence (De Oliveira 2009). The sample size in this study (500 patients per group) provided 90% power to detect a 2% difference in the infection rate (assuming an alpha error of 5%). In trials with a short follow-up (i.e. seven days or less), ITT analysis was performed. The majority of the trials evaluated the incidence of infection over a longer time period (i.e. more than six months). The trialists' definitions of infection were similar and included fever and presence of leukocytes, along with local redness, and exudate or pus at the wound site. A number of these definitions, however, did not include bacterial culture of the wound site. It is worth noting that the following studies met the definition of SSI as defined by the CDC and as detailed in the background section above: (Horan 2008): (Bluhm 1985) (Bluhm 1986); (De Lalla 1990); (De Oliveira 2009); and (Muers 1981).

Allocation

No study described how patients were allocated (i.e. how the randomisation sequence was generated). No trials described how allocation was concealed.

Blinding

Patient blinding

Patients were blinded to treatment allocation in four studies (Bluhm 1985; Bluhm 1986; Chaudhry 2005; De Oliveira 2009). In one trial patients were not blinded (Mounsey 1994). In all remaining trials, blinding of patients was not stated.

Physician blinding

Physicians were blinded to treatment allocation in three studies (Bluhm 1985; Bluhm 1986; Dwivedi 2009), but were not blinded to it in two studies (Chaudhry 2005; Mounsey 1994). In all remaining trials, blinding of physicians was not clear.

Clinician blinding to treatment outcome

In one study clinicians examining patients at follow-up were not blinded to treatment allocation (Chaudhry 2005). In all the remaining trials, it was unclear whether the clinician examining patients at follow-up was blinded to treatment allocation.

Incomplete outcome data

Two studies did not account for all data (Lüninghake 1993; Ucchino 1982). With Lüninghake 1993, data were not available

as the study was reported as an abstract. With Ucchino 1982, the reason for incomplete data was not reported in the study.

Selective reporting

Intention-to-treat (ITT) analysis

For all studies it was not clear whether an ITT analysis was performed, or not.

Other potential sources of bias

Risk of bias summary: Figure 1; Figure 2

Effects of interventions

Results of each comparison category are shown in the analyses. We accepted there was variation in the reported definition of CRMD infection (the main outcome measure), but considered these definitions of infection to be consistent enough to warrant pooling of data. Secondly, while the antibiotic prophylaxis regimens varied amongst studies (on type, dosage, timing, and duration), we believe that all the studies utilised antibiotics that were sufficiently effective against the likely micro-organisms that are implicated in these types of infections (i.e. *Staphylococcal* species, Baddour 2010).

1. Perioperative IV antibiotics (PIVA) compared with no antibiotics

Primary outcomes

Data from six RCTs (1,766 participants) were pooled (I^2 = 0%) comparing PIVA with no antibiotics (Bluhm 1984; Bluhm 1986; De Oliveira 2009; Glieca 1987; Lüninghake 1993; Mounsey 1994). There was a statistically significant reduction in the incidence of SSIs associated with PIVA (RR 0.13; 95% CI 0.05 to 0.36; P value < 0.0001) (Analysis 1.1). Only one of the six RCTs (Bluhm 1984, 100 participants) reported adverse events ; with three events occurred in the antibiotic group (who received cloxacillin) and none in the control group. The adverse events consisted of two cases of diarrhoea and one case of exanthema (skin disruption). This difference was not statistically significant (RR 9.00; 95% CI 0.37 to 162.89; P value 0.14) (Analysis 1.2).

Secondary outcomes

Furthermore, in an analysis of the risk of infection in first-time implants compared with replacement CRMD implants, two trials were pooled (based on I^2 = 39%) and there was no statistically significant difference between the groups (RR 1.55; 95% CI 0.09 to 25.35; P value 0.76) (Analysis 1.3).

No healthcare costs were reported for any of the trials in this comparison. Risk of bias was deemed to be high because a large proportion of the information required to make a judgement was unavailable.

2. PIVA plus local antiseptic wound infiltration compared with PIVA

Primary outcomes

One study examined the effect of perioperative PIVA plus local antiseptic infiltration (infiltration defined as a flushing of the open wound with a syringe) compared with PIVA (Chaudhry 2005). This study demonstrated that the addition of local antiseptic infiltration appeared to have no effect on reducing infections (RR 1.66; 95% CI 0.15 to 18.11; P value 0.68) (Analysis 2.1) This trial was deemed to be at high risk of bias because much of the information required to make the judgement was either not available, or was assessed as being indicative of a high risk of bias.

Secondary outcomes

No healthcare costs were reported for this comparison.

3. PIVA compared with intraoperative local antibiotics

Primary outcome

Two studies comparedPIVA with intraoperative local antibiotics (Bluhm 1985; Ucchino 1982). Their data were pooled (on the basis of I^2 = 0%) The Ucchino trial compared parenteral PIVA with cephalosporins to local intraoperative antibiotic prophylaxis that comprised intraoperative washing of the generator pocket with rifampicin solution just prior to closing the surgical wound. The Bluhm 1985 trial compared PIVA with flucloxacillin to local intraoperative prophylaxis where dextran emulsion with cloxacillin was instilled into the pacemaker pocket prior to closing. No statistical difference was found in comparing systemic antibiotics with local antibiotics in reducing the infection rate (RR 0.45; 95% CI 0.10 to 2.03; P value 0.30) (Analysis 3.1).

Secondary outcomes

No healthcare costs were reported for either of the trials in this comparison. Risk of bias in these trials was deemed to be high because a large part of the information required to make the judgement was unavailable.

4. PIVA plus local intraoperative antibiotics compared with local intraoperative antibiotics alone

Primary outcome

One study examined the effect of PIVAplus local intraoperative antibiotics compared with local intraoperative antibiotics alone (Ramsdale 1984). The interventions were PIVA and oral perioperative antibiotics (cloxacillin with amoxicillin and ampicillin/floxacillin (Magnapen), plus local intraoperative antibiotics (a spray containing neomycin, bacitracin and polyuxom B) sprayed into the pacemaker pocket before generator insertion, compared to local intraoperative antibiotic spray alone,

which was applied in the same manner in both arms of the trial. No significant difference was found in infection rate (RR 0.65; 95% CI 0.27 to 1.53; P value 0.32) (Analysis 4.1). Adverse events were also examined in this trial, and no statistical difference was exhibited between the two treatment groups (RR 11.45; 95% CI 0.64 to 207.57; P value 0.10) (Analysis 4.2). The adverse events noted in the trial were due to side effects of vancomycin in three participants (i.e. hypotension, sweating, nausea, paraesthesia and erythematous skin rash), IV penicillin in one participant (i.e. transient hypotension and skin rash), and one death due to septicaemia from both *Staphylococcus aureus and Candida albicans* in the PIVA group.

Secondary outcomes

No healthcare costs were reported for this comparison. Risk of bias in this trial was deemed to be high because a large proportion of the information required to make a judgement was unavailable.

5. PIVA plus local intraoperative antibiotics compared with PIVA

Primary outcome

One study examined the effect of PIVA (teicoplanin) plus local intraoperative antibiotics (gentamicin solution irrigation just prior to closure of incision) compared with PIVA (teicoplanin) alone (Dwivedi 2009). There was no significant difference in rates of SSI however this comparison is underpowered with only 10 events in total: (RR 1.34; 95% CI:0.39 to 4.64; P value 0.64) (Analysis 5.1).

Secondary outcomes

No healthcare costs were reported for this trial. Risk of bias was deemed to be high because a large proportion of the information required to make a judgement was unavailable.

6. Comparisons between alternative antibiotics

Primary outcome

Only one trial compared different parenteral antibiotics (cephalosporins versus tetracycline) (Ucchino 1982). The numbers in each group were very small and no significant difference was found in infection rates (RR 0.73; 95% CI 0.05 to 10.78; P value 0.82) (Analysis 6.1).

Secondary outcomes

No healthcare costs were reported for this comparison. Risk of bias in this trial was deemed to be high because a large proportion of the information required to make a judgement was unavailable.

7. Duration of antibiotic prophylaxis administration

Primary outcome

The effect of varying the duration of antibiotic prophylaxis (two days versus seven days) was examined in the Dwivedi 2001 study. There was no significant difference in rates of SSI (RR 0.75; 95% CI 0.13 to 4.38; P value 0.75) (Analysis 7.1).

Secondary outcomes

No healthcare costs were reported for this comparison. Risk of bias in this trial was deemed to be high because a large proportion of the information required to make a judgement was unavailable.

8. Comparisons between different antibiotic regimens (different periods of time, routes of administration)

Primary outcome

One trial compared antibiotics administered for different periods of time, i.e. PIVA compared with PIVA plus postoperative antibiotics (De Lalla 1990) (Analysis 7.2). Another trial examined administration of antibiotics at different times, i.e. PIVA compared with a pre-operative antibacterial agent (Lüninghake 1993); while a third investigated the route of antibiotic administration by comparing IV with oral dosing (Morito 2006) (Analysis 8.1). Since there were no infections found in any of the comparison groups, the risk ratios could not be estimated.

Secondary outcomes

No healthcare costs were reported for any of the trials for this comparison. Risk of bias in these trials was deemed to be high as much of the information required to make a judgement was unavailable.

9. Timing of antibiotic administration

Primary outcome

PIVA was compared to postoperative systemic antibiotics in the Walter 1978 study. It was found that PIVA significantly reduced the incidence of infection compared to postoperative antibiotic delivery (RR 0.14; 95% CI 0.03 to 0.60; P value 0.008) (Analysis 10.1). We did not pool the studies of Lüninghake 1993 and Walter 1978 because the timing of the antibiotic administration was too dissimilar.

Secondary outcomes

No healthcare costs were reported for this comparison. Risk of bias in this trial was deemed to be high as much of the information required to make a judgement was unavailable.

10. Perioperative antibiotics compared with local antiseptics

Primary outcome

A perioperative antibacterial agent (type, amount, timing of administration unknown) was compared with no perioperative antibacterial(Lüninghake 1993). Since the type of antibacterial agent was unknown, the authors decided not to include these results in the first comparison above, as the findings would not have been any different by including this trial in the comparison made. There was no statistical difference between the two treatment arms of the trial (RR 0.58; 95% CI 0.02 to 14.13; P value 0.74) (Analysis 11.1).

Secondary outcomes

No healthcare costs were reported for this comparison. Risk of bias in this trial was deemed to be high as much of the information required to make a judgement was unavailable.

Dealing with missing data

In the methods section it was stated that missing data (such as cost data) would be dealt with by imputing replacement values using the average of all observations made after the missing values (post) , or the last observation carrier forward (LOCF) if no following assessments were made. We had planned to do this if there were missing data (i.e. missing cost data), but since there was no cost data available or other missing data, there was no need to perform this type of analysis.

Discussion

A number of combinations of antibiotic prophylaxis and local antiseptics have been examined in the literature including: types of antibiotics used (including combinations of); timing of administration; duration, cessation, and route of administration.

The most extensively studied comparison has been the use of systemic antibiotic prophylaxis plus local antiseptics compared with no antibiotic (assumed use of a local antiseptic only), with antibiotic prophylaxis delivered perioperatively (typically PIVA) an hour or less before the procedure. As noted, this combination has demonstrated a significant reduction in the incidence of infections. This finding is in line with the recent recommendations for antibiotic prophylaxis from the AHA, also endorsed by the Heart Rhythm Society (Baddour 2010). As well, and in line with findings from Bratzler 2004 and Classen 1992, perioperative antibiotic prophylaxis delivered within the hour prior to CRMD implantation, demonstrated a significant reduction on the infection rate when compared to postoperative delivery of antibiotic.

Three of the included studies examined the effect of antibiotic prophylaxis within a period of seven, or fewer, days after surgery (Glieca 1987; Morito 2006; Walter 1978). Since the majority of the studies examined the incidence of infection over longer time frames, these studies may have underestimated the true incidence of infection with CRMD implants.

Consideration should be given as well, to the issue of formation of biofilm on the CRMD implant, which is known to develop in more than 25% of device implants (Hazan 2006), and its potential for latent infection. As outlined above, biofilms form a protective environment for micro-organisms, and can make them more resistant to the effects of short-term systemic antibiotic prophylaxis. The bacteria within biofilms can also remain quiescent in the biofilm for years before clinical presentation. The sequelae of this quiescence might be demonstrated in the fact that a significant portion of CRMD-related infections occur months after hospital discharge. Some have postulated that the administration of local perioperative antibiotic prophylaxis (either with systemic antibiotic prophylaxis or alone), or even local antiseptic infiltration of the pacemaker pocket may reduce the incidence of biofilm formation on CRMD implants. Unfortunately the administration of local antibiotic or antiseptic prophylaxis either delivered concomitantly with systemic antibiotic prophylaxis, or as monotherapy, did not demonstrate a reduction in the infection rate seen with systemic antibiotic monotherapy (local versus systemic includes: Bluhm 1985; Ucchino 1982; local versus systemic plus local includes: Ramsdale 1984; systemic versus. systemic plus local includes: Dwivedi 2009 and; local antiseptic infiltration plus systemic antibiotic versus systemic antibiotic includes: Chaudhry 2005). These trials were probably too underpowered to be able to demonstrate a difference. Furthermore, it is likely that infiltration of the pacemaker pocket with local antibiotic or local antiseptic does not address the issue of biofilm formation on the CRMD implant. Biofilm formation occurs at the time of CRMD implantation, and probably develops from the flora on the patient's skin (*Staphylococcus epidermis*), or possibly from the caregiver's hands. *S epidermis* is a slime-producing bacterium which plays a significant part in biofilm formation. Furthermore, hydrophilic antibiotics such as cephalosporins and vancomycin, which were used in a large number of the included studies, do not penetrate well into colonised areas such as biofilms (Darouiche 1994; Souli 1998). Consequently, the issue of biofilm prevention requires further investigation and evaluation. The issue of biofilm may be especially important for patients who are immunosuppressed, or have diabetes mellitus, congestive heart or renal failure, suffer from skin disorders, or are malnourished (and thus at higher risk for infection).

One of the main issues that requires attention (mentioned in "Description of the condition") is the recent, accelerated rate of CRMD infections. This analysis reaffirms the need for perioperative antibiotic prophylaxis as part of the surgical implant procedure. This recommendation, however, has only recently appeared in clinical guidelines (first appearing in 2008; SIGN 2010). Adherence to the guidelines based on these findings is of paramount importance. In general, adherence to guidelines such as these have been sub-optimal - even for general surgery, where they have been in place for several years (Bratzler 2004). Reports from government agencies such as the US Agency for Healthcare Research and Quality (AHRQ) have shown adherence to this type of guideline has been sub-optimal (Ranji 2007). Perioperative antibiotic prophylaxis for CRMD implants should be part of a comprehensive surgical-site infection program administered at any hospital, and monitoring and reporting of adherence should be part of this program.

We did not find any studies that examined the effect of infections on overall healthcare costs, however, considering that there are close to 800,000 CRMDs implanted annually, with infection rates approaching 5.3% (estimated 42,400 infections yearly), and costs approaching USD 80,000 per implant to treat each infection, this results in a significant drain on the overall

worldwide healthcare system resources (estimated cost of USD 3.5 billion a year to treat these infections).

One of the issues that could not be examined sufficiently, because its use was not clearly stated in many of the trials, was local skin antisepsis as part of perioperative prophylaxis. It is interesting to note that, in a recent prospective randomised trial published in the New England Journal of Medicine, preoperative cleansing of a patient's skin with chlorhexidine-alcohol was superior to cleansing with povidone-iodine for preventing surgical-site infection (Darouiche 2010).

Methodological rigor in designing trials to ensure a minimal risk of bias in the results was not described well within the majority of the studies. This was due to several trials having been published in abstract form only (Chaudhry 2005, Dwivedi 2009, Lüninghake 1993), and an inability to obtain additional information from the authors. Secondly, several of the published trials were published more than 20 years ago, which made it difficult to find contact information for the authors in order to follow-up with questions related to assessment of bias (Bluhm 1984, Bluhm 1985, Glieca 1987, Ramsdale 1984, Walter 1978).

Despite the bias limitations outlined above, and as mentioned above, these findings were remarkably similar to a landmark study on the use of antibiotic prophylaxis in surgery (Classen 1992).

Summary of main results

- Perioperative IV antibiotic (PIVA) prophylaxis plus antiseptics (delivered within the hour before the procedure) is effective at reducing infections seen with CRMD implantation.
- The number of infections is related to the timing of antibiotic prophylaxis; with postoperative antibiotic prophylaxis showing a significantly higher infection rate than perioperative antibiotic prophylaxis delivered within the hour before the procedure.

Overall completeness and applicability of evidence

We believe that this analysis is the most comprehensive and up-to-date, review of prospective randomised studies related to CRMD implants. The strength of the evidence, especially as it relates to perioperative antibiotic prophylaxis warrants consideration of incorporation of perioperative antibiotic prophylaxis as part of every CRMD implantation procedure.

Quality of the evidence

The quality of the evidence in the included studies was poor . This judgement was made because much of the information required for assessing bias was not available for evaluation.

Potential biases in the review process

While an attempt was made to identify every prospective randomised trial, both published and non-published, irrespective of language in which written, we cannot guarantee that there are no other available studies that could have been evaluated. We identified 16 trials from a wide range of countries that perform this procedure including: Brazil (one trial); Germany (two trials); India (two trials); Italy (three trials); Japan (1 trial); Sweden (three trials); United Kingdom (two trials); and the United States (one trial). We also identified several studies in both Italian and German which we had translated. Therefore, we believe language and location bias were minimised. Regarding publication bias, although we asked manufacturers and distributors of antibiotics about these types of studies, we did not identify any additional ones through this route. Nonetheless, we cannot guarantee that trials with negative outcomes, such as an increase in adverse events with use of antibiotics, or an increase in infections with various other types of antibiotics, do not exist.

Agreements and disagreements with other studies or reviews

This analysis is a more extensive and complete analysis than the meta-analysis performed by Da Costa 1998. It includes a number of studies that were published after the Da Costa analysis (Chaudhry 2005; De Oliveira 2009; Dwivedi 2001; Dwivedi 2009; Morito 2006), and includes studies that were not evaluated in the Da Costa study as well (Bluhm 1985; De Lalla 1990; Ucchino 1982; Walter 1978). The Da Costa analysis appears only to have examined the comparison of systemic antibiotics versus no antibiotics. This analysis goes further and examines a variety of comparisons of combinations of antibiotics, timing, routes of administration, dosages, and durations of antibiotic prophylaxis in prospective randomised trials. We believe this analysis builds upon the findings of the Da Costa meta-analysis, and reaffirms its findings, namely; that perioperative systemic antibiotic (PSA) prophylaxis has a significant protective effect (RR 0.13; 95% CI 0.05 to 0.36; P value less than 0.00001). This analysis also reaffirms the findings of Classen 1992, namely that perioperative antibiotic prophylaxis delivered during the hour prior to the procedure was superior to antibiotics administered postoperatively.

Authors' conclusions

Implications for practice

There is strong evidence that perioperative prophylactic antibiotics (administered in the hour prior to the procedure) reduce the risk of surgical site infection in people undergoing CRMD implantation.

Implications for research

Further studies are needed to explore the use of local antibiotic and antiseptic prophylaxis (e.g. within the CRMD surgical pocket as well as on the CRMD implant itself, or on the CRMD implant alone) and its effect on the formation of biofilm on CRMD implants and CRMD implant-related infections. The costs to treat these types of infections also require further analysis in properly designed trials. Finally, given the poor quality of the trials, future trials should be well-designed and follow the CONSORT statement for the reporting of RCTs. Well designed trials would include the following study designs and endpoints:

- Study designs:
  - ensuring the blinding of clinical assessors and patients on the outcome of infection
  - perform power calculations prior to study initiation on the patient population(s) to be studied in order to generate statistically meaningful results.
- Study endpoints:
  - evaluation of patients on the infection endpoint over a longer timeframe than one year in order to ensure that the effects of biofilm on the infection rate is evaluated (as biofilms may remain dormant for extended periods of time before and infection is diagnosed).

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Contributions of authors

Rabih Darouiche and Michael Mosier: conceived the review question, developed the protocol and performed part of writing or editing of the protocol and review. Made an intellectual contribution to the review, and approved final versions of the protocol and review prior to submission.
Jeffrey Voigt: conceived the review question, developed the protocol and review, co-ordinated the protocol and review development, and completed the first draft of the protocol and review. Made an intellectual contribution to the review, and approved final version of the review prior to submission. Made all of the changes suggested by the reviewers in the final draft.
Michael Mosier: conceived the statistical analysis protocol. Reviewed all of the statistical analysis prior to submission.
All authors are guarantors of the review.

Contributions of editorial base

Nicky Cullum: edited the review, advised on methodology, interpretation and review content. Approved the final review prior to submission.
Sally Bell-Syer: co-ordinated the editorial process. Advised on methodology, interpretation and content. Edited the review.
Ruth Foxlee: designed the search strategy, ran the searches and edited the search methods section.

Declarations of interest

Rabih Darouiche and Michael Mosier: none to declare.

Jeffrey Voigt: works as a reimbursement consultant for medical technology companies and has worked in the past for a client who has developed a drug/device combination product for use in preventing CRMD-related infections. This author recently drafted a review of "good antimicrobial" stewardship for use with an FDA filing for this company.

Differences between protocol and review

In the Types of interventions section, we added the following type of interventions:

- systemic antibiotic plus local antiseptic compared with local antibiotic plus local antiseptic;
- systemic antibiotic plus local antibiotic compared with local antibiotic; and
- comparison of different routes of administration.

Subgroup analysis refinement included: infection rate in primary versus replacement CRMDs, and infection rate by operator experience (inexperienced versus experienced).

Infection rate seen post discharge was extended from up to six months to six months or longer.

Specific hypotheses were added post protocol after analysis of the studies showed variations in timing of antibiotic prophylaxis, type of antibiotic prophylaxis administered, type of implant (pacemaker versus cardioverter-defibrillator), primary versus replacement implant, and the route by which the antibiotic was delivered (e.g. systemic IV, local, oral).

Published notes

Characteristics of studies

Characteristics of included studies

De Lalla 1990

Methods	Single-centre trial, country of origin: Italy. A priori power calculation: no. Reliable primary outcome: yes. Average length of follow-up on 505 patients 20.1 months (range: 12-36 months).
Participants	Male and female patients undergoing primary pacemaker and electrode implantation. All pacemakers placed in a subcutaneous prepectoral pocket; cephalic or occasionally subclavian veins used for insertion of electrode. Unclear if informed consent obtained. Average age: Group A = 71.4 years; Group B = 70.9 years. Exclusion criteria: signs or symptoms of infection; received antibiotics within last 5 days; allergy to betalactams and/or aminoglycosides. Total number of patients randomised to trial: 552.
Interventions	Group A: perioperative (15-20 minutes prior to procedure) IV bolus 2 g mezlocillin and 200 mg netilmicin (n = 255). Group B: as for Group A, plus 200 mg netilmicin and 2 g mezlocillin 6 h and 12 h post procedure along with 200 mg netilmicin 12 h post procedure (n = 250). Both treatment groups: operating field disinfected with 0.5% chlorhexidine in 70% ethyl alcohol.
Outcomes	Incidence of infection: early infection defined as evidence of acute inflammation (redness, swelling and/or appearance of a serous-purulent discharge), with or without raised temp (> 37.5 ^{o}C), on at least 2 separate occasions, and laboratory evidence of infection (leukocytosis, increased sedimentation rate), with or without potential pathogens isolated from pocket discharge. Late infection defined as symptoms of early infection with additional fever associated with positive blood culture of inexplicable origin.
Notes	Disclosures not noted. No adverse/allergic reaction events were noted in either group, though 95 patients died; 45 in Group A and 50 in Group B. 47/95 of these patients died 2-12 months after implantation, and were not evaluated for incidence of infection. No allergic reaction to mezlocillin or netilmicin noted.

Risk of bias table

Item	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear	Not stated - study was stated to be "randomised" but did not report the method of sequence generation.
Allocation concealment?	Unclear	Study did not mention whether allocation to particular intervention groups was concealed.
Blinding? All outcomes - patients	Unclear	Study did not mention whether patients were blinded to the intervention.
Blinding? All outcomes - intervention providers	Unclear	Study did not mention whether physicians administering antibiotic prophylaxis were blinded to the intervention given.
Blinding? All outcomes - outcome assessors	Unclear	Study did not mention whether physicians evaluating patients for the presence or absence of an infection were blinded to the intervention given.
Incomplete outcome data addressed?	Yes	Data on those patients who died prior to the required follow-up assessment period of at least 1 year were excluded from analysis.
Free of selective reporting?	Unclear	There was insufficient information to permit judgement of ‘Yes’ or ‘No’ on this parameter. The trial protocol was not available to help us evaluate this.
Free of other bias?	Unclear	Other risks of bias were not noted in the trial.

Walter 1978

Methods	Single-centre trial; country of origin: Germany. A priori power calculation: no. Reliable primary outcome: yes. Length of follow-up: 6 days.
Participants	Gender of participants unknown. Patients undergoing primary pacemaker implantation and generator change. All pacemakers placed in pectoral region (communications with translator). Unclear if informed consent obtained. Average age 66 years. Trial exclusion criteria: unclear. Total pacemaker (primary and replacement) implant participants randomised to trial = 100.
Interventions	Group A: (PSA) 4 g cephalothin IV 1 h prior to procedure and 4 g cephalothin IV bid for 2 days. 40 patients had primary pacemaker implant and 10 had generator change (n = 50). Group B: (postoperative antibiotic prophylaxis) 4 g cephalothin IV post procedure tid for 2 days. 40 patients had primary pacemaker implant and 10 had generator change (n = 50).
Outcomes	Incidence of infection: infection defined in terms of raised body temperature, leukocyte counts, urea and creatinine, delayed wound healing, adverse events. Leukocytes were measured via laboratory.
Notes	Disclosures not noted. Unclear whether local skin antisepsis performed perioperatively, but, based on standard of care, this was assumed to be the case. Adverse events included mild temporary increases in serum urea levels but no allergic reactions to the antibiotics. No participants appear to have been excluded from trial and analysis.

Risk of bias table

Item	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear	Not stated - study was stated to be "randomised" but did not report the method of sequence generation.
Allocation concealment?	Unclear	Study did not mention whether allocation to the particular intervention group was concealed just prior to administering it.
Blinding? All outcomes - patients	Unclear	Study did not mention whether patients were blinded to the intervention.
Blinding? All outcomes - intervention providers	Unclear	Study did not mention whether physicians administering the antibiotic prophylaxis were blinded to the intervention given.
Blinding? All outcomes - outcome assessors	Unclear	Study did not mention whether physicians evaluating patients for the presence or absence of an infection were blinded to the intervention given.
Incomplete outcome data addressed?	Yes	Not directly addressed in study. However, there appear to have been no patients with incomplete data.
Free of selective reporting?	Unclear	There was insufficient information to permit judgement of ‘Yes’ or ‘No’ on this parameter. The trial protocol was not available to help us evaluate this.
Free of other bias?	Unclear	Other risks of bias were not noted in the trial.

Ucchino 1982

Methods	Single-centre trial; country of origin: Italy. Power calculation: no. Reliable primary outcome: yes. Length of follow-up not reported. Loss to follow up not reported .Missing data not reported.
Participants	Male and female patients undergoing permanent pacemaker replacement (including generator replacement only). Average age 71 years (range 56-81 years). Exclusion criteria: concurrent infection at time of surgery; diabetes; antibiotic treatment in days prior to intervention. Total pacemaker implant patients randomised to trial = 72.
Interventions	Group A: parenteral cephalosporin (cefamandole, cefoxitin, cefotaxime, or cefuroxime) 1 g at time of intervention followed by 2 further 1 g doses 6 h and 12 h post surgery (n = 22). Group B: pocket washed with rifampicin solution at the time of surgery (n = 34). Group C: parenteral tetracycline 150 mg q 8 h for 48 h (n = 16). Co-interventions: percutaneous drainage placement.
Outcomes	Incidence of infection: infection defined as clinical signs and symptoms of infection (including increased local temperature, redness, pain, swelling, and presence of purulent discharge. Systemic signs of infection included increasing total leukocyte count, fever, and/or bacteraemia) along with microbiological assessment (swab from wound, or blood cultures).
Notes	Disclosures not noted. Adverse reactions to intervention not noted. Timing of initial parenteral (perioperative) antibiotic administration and method of delivery (e.g. IM or IV) were unclear. Location of pacemaker placement (i.e. abdominal vs pectoral) unclear. Description of analysis employed not reported. No baseline comparisons reported. Methodological quality of study was poor. Based on definitions of the type of intervention(s), a decision was made by the authors to group them as follows: Group A and Group C grouped as PSA plus local antiseptic, and Group B considered as perioperative local antibiotic plus local antiseptic in analysis section below for one analysis (#2 in data & analysis section). An additional analysis was performed on the type of perioperative systemic antibiotic (cephalosporin) vs type of perioperative systemic antibiotic (tetracycline) (#5 in data & analysis section).

Risk of bias table

Item	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear	Not stated - study was stated to be "randomised" but did not report the method of sequence generation.
Allocation concealment?	Unclear	Study did not mention whether allocation to the particular intervention group was concealed just prior to administering it.
Blinding? All outcomes - patients	Unclear	Study did not mention whether patients were blinded to the intervention.
Blinding? All outcomes - intervention providers	Unclear	Study did not mention whether physicians administering the antibiotic prophylaxis were blinded to the intervention given.
Blinding? All outcomes - outcome assessors	Unclear	Study did not mention whether physicians evaluating patients for the presence or absence of an infection were blinded to the intervention given.
Incomplete outcome data addressed?	Unclear	Study did not address issue of incomplete outcome data.
Free of selective reporting?	Unclear	There was insufficient information to permit a judgement on this parameter. The protocol was not available to help us evaluate this.
Free of other bias?	Unclear	Other risks of bias were not noted in the trial.

Bluhm 1984

Methods	Single-centre trial; country of origin: Sweden. ITT: no. A priori power calculation: no. Reliable primary outcome: yes. Length of follow-up: 7-43 months.
Participants	Male and female participants. Average age; (SD): Group A = 71.2; (10.7) years; Group B = 74.4; (10) years. Group A = 24 patients with 1 implantation in the same generator pocket; 16 with 2 implantations in the same generator pocket; 6 with 3 implantations; 3 with 4 implantations, and 2 with > 4 implantations. Trial exclusion criteria: signs of current infection; receiving antibiotic therapy that could interfere with the prophylaxis. Total participants randomised to trial = 123, however, 23 were excluded (see notes section).
Interventions	All participants: preoperative skin disinfection - whole body washed 1-3 days preoperatively with Hibiscrub containing 4% chlorhexidine gluconate. Immediately prior to operation, the operative field was shaved and washed once more with Hibiscrub and then with 0.5% chlorhexidine in 70% ethyl alcohol. Group A: (PSA) cloxacillin 2 g IV 1-2 h preoperatively then 1 g every 6 h postoperatively for 2 days, followed by the same dose perorally for 8 more days (n = 50). Group B: preoperative skin disinfection (as above) only (n = 50).
Outcomes	Incidence of infection: infection diagnosed via bacterial culture from a specimen taken from wound margins postoperatively. In febrile patients, blood was also taken for culture. Criteria for local infection (at site of implant) upon discharge was presence of purulent substance and/or increased local temperature, redness, pain, and swelling. Local infection was judged independently by 2 physicians. Patients were examined on the 10th postoperative day, at 1 month, and then every 6 months.
Notes	Disclosures not noted. Adverse reactions to antibiotics were noted in Group A including: diarrhoea (n = 2) and exanthema (n = 1). 123 patients randomised: 23 excluded and not included in the analysis because of large haematoma (n = 9); reoperation within 1 month (n = 6); antibiotic treatment for other reasons within 1 month (n = 4); death from intercurrent disease within 1 month (n = 3). More patients with 2 or more implantations in the same generator pocket in Group B (n = 33) than Group A (n = 27). Generators placed in the subcutaneous abdominal pocket; right cephalic or right external jugular vein used for IV electrode.

Risk of bias table

Item	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear	Not stated - study was stated to be "randomised" but did not report the method of sequence generation.
Allocation concealment?	Unclear	Study did not mention whether allocation to the particular intervention group was concealed just prior to administering it.
Blinding? All outcomes - patients	Unclear	Study did not mention whether patients were blinded to the intervention.
Blinding? All outcomes - intervention providers	Unclear	Study did not mention whether physicians administering the antibiotic prophylaxis were blinded to the intervention given.
Blinding? All outcomes - outcome assessors	Unclear	Study did not mention whether physicians evaluating patients for the presence or absence of an infection were blinded to the intervention given.
Incomplete outcome data addressed?	No	Of 123 patients randomised, 23 were excluded and not included in the analysis because of large haematoma (n = 9); reoperation within 1 month (n = 6); antibiotic treatment for other reasons within 1month (n = 4); death from intercurrent disease within 1 month (n = 3)
Free of selective reporting?	No	23 patients were excluded from trial after being randomised and no mention was made of their results.
Free of other bias?	Unclear	Other risks of bias were not noted in the trial.

Ramsdale 1984

Methods	Single-centre trial; country of origin: United Kingdom. ITT: no. A priori power calculation: no. Reliable primary outcome: yes. Length of follow-up: 1 year.
Participants	Male and female participants. Average age; (SD): 73.4; (10.7) years for treatment group (IV systemic and local antibiotic); 71.4; (11.9) years for control group (local antibiotic). Trial included 4 groups A-D, which had different procedures: Group A = first pacemaker implant; Group B = generator replacements only; Group C = removal of entire system (pacemaker and lead) and implant of new system; Group D = abdominal procedures. Trial exclusion criteria: not stated, however, 530 patients considered for the study, but only 500 randomised. Total participants randomised to trial = 500. 12.5% of the patients enrolled in trial had missing data at 6-month follow-up; 43% of patients had missing data at 1-year follow-up.

Interventions	All participants: night prior to procedure, patients' skin over anterior chest wall and axillae (or abdomen if an abdominal procedure was planned) painted with 10% alcoholic solution of povidone iodine. Patients' skin further repainted with povidone-iodine solution and washed with 0.5% alcoholic chlorhexidene before local anaesthesia administered. Intervention arm: (PSA) cloxacillin 1 g plus amoxicillin 1 g intravenously 1 h prior to procedure plus ampicillin/floxacillin (Magnapen) 500 mg orally every 6 h for 48 h starting 1 h post implantation. Lastly antibiotic spray containing neomycin (500,000 units), bacitracin (17,500 units) and polyuxom B (150,000 units) was sprayed into the pacemaker pocket before generator insertion and the subcutaneous tissue was sutured. Patients allergic to penicillin received vancomycin 1 g diluted in 150 ml of 5% dextrose IV 1 h preoperatively plus erythromycin 500 mg orally every 6 h for 48 h commencing 1 h post implantation (n = 244). Control arm: antibiotic spray containing neomycin (500,000 units), bacitracin (17,500 units) and polymyxin B (150,000 units) was sprayed into the pacemaker pocket before generator insertion and the subcutaneous tissue was sutured (n = 256).
Outcomes	Incidence of infection: defined in 1 of 2 ways: 1) pocket infection: temperature > 37.5 ^{o} C on 2 or more occasions on, or after, the 3rd postoperative day, associated with acute inflammation around generator and/or pus in the generator pocket; 2) superficial wound inflammation: indurated discharging and non-discharging wound edges without evidence of pocket infection, requiring antibiotic treatment, but not generator replacement.
Notes	Disclosures not noted. Adverse reactions to interventions were noted, including side effects to vancomycin (hypotension, sweating, nausea, paraesthesia and erythematous skin rash, n = 3), and penicillin (transient hypotension and skin rash, n = 1). 1 death due to septicaemia from both *Staphylococcus aureus* and *Candida albicans* in the PSA group. Therefore a total of 5 adverse events occurred in the PSA (intervention) group. The following were also noted: Control arm: diabetes (n = 4); corticosteroid use (n = 3). Treatment arm: diabetes (n = 4); corticosteroid use (n = 3). NS. Of the pacemakers implanted: • 369 = 1st implants placed in the pectoral region (n = 183 PSA + local antibiotic vs n = 186 local antibiotic only). 4 infections in PSA + local antibiotic group vs 10 in local antibiotic group. • 87 = generator replacements in the pectoral region (n = 42 PSA + local antibiotic vs n = 45 local antibiotic only). 1 infection in the PSA and local antibiotic group vs 0 in the local antibiotic group. • 31 = removal of an old generator and replacement with a new system in the pectoral region (generator plus lead) (n = 13 PSA + local antibiotic vs n = 18 local antibiotic group). No infections in either group. • 13 abdominal implant procedures (n = 6 PSA + local antibiotic vs n = 7 local antibiotic). There were no infections in the PSA + local antibiotic group vs 1 infection in the local antibiotic group. 2/5 operators implanting pacemakers were inexperienced and it was not noted which patients were treated by them. Significant amount of missing data (43%) at 1-year follow-up. Methodological quality of study: poor.

Risk of bias table

Item	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear	Not stated - study was stated to be "randomised" but did not report the method of sequence generation.
Allocation concealment?	Unclear	Study did not mention whether allocation to the particular intervention group was concealed just prior to administering it.
Blinding? All outcomes - patients	Unclear	Study did not mention whether patients were blinded to the intervention.
Blinding? All outcomes - intervention providers	Unclear	Study did not mention whether physicians administering the antibiotic prophylaxis were blinded to the intervention given.
Blinding? All outcomes - outcome assessors	Unclear	Study did not mention whether physicians evaluating patients for the presence or absence of an infection were blinded to the intervention given.
Incomplete outcome data addressed?	No	12.5% of patients enrolled in trial had missing data at 6-month follow-up; 43% had missing data at 1-year follow-up.
Free of selective reporting?	No	12.5% of patients enrolled in trial had missing data at 6-month follow-up; 43% had missing data at 1-year follow-up.
Free of other bias?	Unclear	Other risks of bias were not noted in the trial.

Bluhm 1985

Methods	Single-centre trial; country of origin: Sweden. A priori power calculation: no. Reliable primary outcome: no. Definition of infection not clearly stated in the methods section, however, it appears that the definition used included: local pain, redness, increased local temperature, swelling, and positive tissue fluid culture (culture performed on all patients). Length of follow-up: 7-38 months.
Participants	Male and female participants undergoing generator replacement. Implant in pectoral region. Informed consent obtained for those enrolled in trial. Average age: Group A = 74.7 years; Group B = 73.5 years. Trial exclusion criteria: signs of current infection, or treatment with antibiotics that would interfere with the prophylaxis. Total replacement pacemaker implant participants randomised to trial = 108: 3 excluded after randomisation, 2 due to incorrect codification and 1 because < 1 month follow-up (death 8 days postoperatively due to congestive heart failure).
Interventions	Group A: (PSA) flucloxacillin 2 g IV 1 h preoperatively for 20 minutes and then 1 g flucloxacillin orally every 8 h postoperatively for 5 days (n = 53). Group B: 10 ml dextran emulsion with cloxacillin 50 mg/ml instilled into pacemaker pocket prior to closing. Patients also received IV infusion of 0.9% sodium chloride preoperatively and an oral placebo for 5 days postoperatively (n = 52). Both treatment groups: operating field disinfected with 0.5% chlorhexidine in 70% ethyl alcohol immediately before surgery.
Outcomes	Incidence of infection: infection defined as: local pain, redness, increased local temperature, swelling, and positive tissue fluid culture (culture performed on all patients).
Notes	Disclosures not noted. Adverse reaction to intervention: prophylaxis shorter for 3 patients in Group A, due to diarrhoea (2) and nausea (1). Patients examined on 10th day after surgery, at least 1 month later, then every 6 months. Range of follow-up: 7-38 months. Majority of patients had received 2 or more implantations (replacement generators) in the same generator pocket (92%).

Risk of bias table

Item	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear	Not stated - study was stated to be "randomised" but did not report the method of sequence generation.
Allocation concealment?	Unclear	Study did not mention whether allocation to the particular intervention group was concealed just prior to administering it
Blinding? All outcomes - patients	Yes	While it is unclear as to who was blinded, it appears that the patients were blinded to the treatment regimen. Under the Patients and methods section (subjects) is was stated that the study was "double-blind".
Blinding? All outcomes - intervention providers	Yes	While it is unclear who was blinded, it appears that the operator (surgeon) was blinded to the treatment regimen. Under Patients and methods section (subjects) is was stated that the study was "double-blind".
Blinding? All outcomes - outcome assessors	Unclear	Study did not mention whether physicians evaluating patients for the presence or absence of an infection were blinded to the intervention given.
Incomplete outcome data addressed?	Yes	3 excluded after randomisation: 2 patients excluded due to incorrect codification and 1 because of < 1 month follow-up (death at 8th day after surgery due to congestive heart failure).
Free of selective reporting?	No	No (2 patients excluded due to incorrect codification and 1 because < 1 month follow-up (death at 8th day after surgery due to congestive heart failure).
Free of other bias?	Unclear	Other risks of bias were not noted in the trial.

Bluhm 1986

Methods	Single-centre trial; country of origin: Sweden. ITT: no (11 patients, 6 in Group A and 5 in Group B withdrawn for reasons predetermined in the study). A priori power calculation: no. Reliable primary outcome: yes. Length of follow-up: 7-35 months.
Participants	Male and female participants undergoing primary pacemaker implantation. Implant in pectoral region. Informed consent obtained for those enrolled in trial. Average age: Group A = 76 years; Group B = 74 years. Trial exclusion criteria: signs of current infection being treated with antibiotics. Total primary pacemaker implant participants randomised in trial = 106; 11 excluded after randomisation; 6 from Group A and 5 from Group B.
Interventions	Group A: (PSA) flucloxacillin 2 g IV administered 1 h preoperatively for 20 minutes, then 1 g flucloxacillin orally every 8 h for 5 days (n = 52). Group B: placebo infusion administered 1 h preoperatively for 20 minutes prior to surgery, then 1 g placebo tablets orally every 8 h for 5 days (n = 54). Both groups: operating field disinfected with 0.5% chlorhexidine in 70% ethyl alcohol immediately before surgery.
Outcomes	Incidence of infection defined as purulent secretion with 2 or more inflammatory signs of: local temperature rise, redness, pain and swelling together with a positive culture; or all 4 inflammatory signs without positive culture.
Notes	Disclosures not noted. Adverse reactions to intervention were not noted. The following were also noted: Group A: diabetes (n = 7); malignant disease (n = 10); alcohol abuse (n = 1); Group B: diabetes (n = 4); leg ulcer (n = 1); indwelling urinary catheter (n = 1); malignant disease (n = 5); alcohol abuse (n = 1).

Risk of bias table

Item	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear	Not stated - study was stated to be "randomised" but did not report the method of sequence generation.
Allocation concealment?	Unclear	Study did not mention whether allocation to the particular intervention group was concealed just prior to administering it.
Blinding? All outcomes - patients	Yes	Patients were blinded to treatment; study stated in introduction that trial was double-blinded.
Blinding? All outcomes - intervention providers	Yes	Yes, however, unclear as to who delivered the intervention and which physician(s) were blinded - the assumption was made that the clinician delivering the antibiotic was blinded to the intervention.
Blinding? All outcomes - outcome assessors	Unclear	Study did not mention whether physicians evaluating patients for the presence or absence of an infection were blinded to the intervention given.
Incomplete outcome data addressed?	Yes	In patients withdrawn after randomisation: 6 in Group A (treatment) and 5 in Group B (control); there were no infections.
Free of selective reporting?	Yes	Reported all outcomes, even for patients withdrawn from randomisation.
Free of other bias?	Unclear	Other risks of bias were not noted in the trial.

Glieca 1987

Methods	Single-centre trial; country of origin: Italy. ITT: unclear. Power calculation: unclear. Reliable primary outcome: yes. Length of follow up: 7 days.
Participants	Male and female participants admitted for 1st implant (pacemaker plus lead) or replacement generator. Average age (SD): Group A = 66.41 (10.15) years; Group B = 65.54 (7.16) years. Implants: Group A = 97 pectoral (right or left), 3 abdominal; 76 primary implants, 24 generator replacements. Group B = 98 pectoral (right or left), 2 abdominal; 79 primary implants and 21 replacements. Trial exclusion criteria: not stated. Total pacemaker implant participants randomised in trial = 200.
Interventions	Group A: cefazolin 4 g/day for 5 consecutive days (n = 100). Group B: no antibiotic (n = 100).
Outcomes	Infection: defined as a temperature above 37.5 ^{o}C after 3rd day combined with signs of inflammation on the wound site or purulent exudate. Groups were evaluated for a total of 7 days.
Notes	No disclosures. We assumed that systemic IV antibiotic was administered during the perioperative period, although the study did not specifically state this. Adverse events or allergic reactions to antibiotic were not noted.

Risk of bias table

Item	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear	Not stated - study was stated to be "randomised" but did not report the method of sequence generation.
Allocation concealment?	Unclear	Study did not mention whether allocation to the particular intervention group was concealed just prior to administering it.
Blinding? All outcomes - patients	Unclear	Study did not mention whether patients were blinded to the intervention.
Blinding? All outcomes - intervention providers	Unclear	Study did not mention whether physicians administering the antibiotic prophylaxis were blinded to the intervention given.
Blinding? All outcomes - outcome assessors	Unclear	Study did not mention whether physicians evaluating patients for the presence or absence of an infection were blinded to the intervention given.
Incomplete outcome data addressed?	Yes	Complete data assessment on patients while in hospital for a total of 7 days.
Free of selective reporting?	Yes	All data points accounted for as patients were evaluated while in hospital over a period of 7 days.
Free of other bias?	Unclear	Other risks of bias were not noted in the trial.

Lüninghake 1993

Methods	RCT; randomisation scheme unclear; single-centre trial; country of origin: Germany. Blinding: unclear. ITT: unclear. A priori power calculation: unclear. Reliable primary outcome: yes. Length of follow-up: 1 year.
Participants	Baseline characteristics of patients included in trial unclear - no mention of sex or age. No mention made of exclusion criteria. Total pacemaker implant patients randomised in trial = 302.
Interventions	Group A (normal risk of infection): (PSA) 2 g cefazedone IV administered 90 minutes prior to the procedure plus local antiseptic perioperatively (n = 107). Group B: perioperative local antiseptic only (n = 106). Group C (elevated risk for infection): (PSA) antistaphylococcal antibiotic administered perioperatively plus local antiseptic perioperatively (n = 29). Group D: these patients were either already being treated with an antibacterial agent for an intercurrent infection, and thus were not given additional prophylaxis, and, if patients were allergic to beta-lactam antibiotics, no further antibiotic was applied. Local antiseptic administered perioperatively. Type of antibacterial agent unknown. (n = 60).
Outcomes	Microbiologically-proven infection.
Notes	Disclosures not noted. Unclear whether local antiseptic was administered prior to the procedures, however, based on standards of surgical care, this was assumed to be the case. Types of intervention(s): duration and time of initiation of interventions for Groups C and D unclear. Pacemaker placement location unclear, also unclear whether implants were primary or replacements. Adverse events to antibiotics not noted. Methodological quality of study: poor.

Risk of bias table

Item	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear	Not stated - study was stated to be "randomised" but did not report the method of sequence generation.
Allocation concealment?	Unclear	Study did not mention whether allocation to the particular intervention group was concealed just prior to administering it.
Blinding? All outcomes - patients	Unclear	Study did not mention whether patients were blinded to the intervention.
Blinding? All outcomes - intervention providers	Unclear	Study did not mention whether physicians administering the antibiotic prophylaxis were blinded to the intervention given.
Blinding? All outcomes - outcome assessors	Unclear	Study did not mention whether physicians evaluating patients for the presence or absence of an infection were blinded to the intervention given.
Incomplete outcome data addressed?	Unclear	Since study was in abstract form, these data were not available.
Free of selective reporting?	Unclear	Since study was in abstract form, these data were not available.
Free of other bias?	Unclear	Other risks of bias were not noted in the trial.

Mounsey 1994

Methods	RCT; randomisation scheme unclear; single-centre trial; country of origin: United Kingdom. Blinding: no. ITT: yes. A priori power calculation: unclear. Reliable primary outcome: yes. Length of follow-up (mean (SD)) = 19 (5) months.
Participants	Male and female patients undergoing pacemaker implantation. Consent obtained for those enrolled in trial. Average age (SD): Group A = 74.3 (11.8) years; Group B = 74.2 (12.6) years. Trial exclusion criteria: patients undergoing pulse generator replacement or electrode change; overt sepsis; patients refusing consent. Total primary pacemaker implant participants randomised in trial = 473.
Interventions	Group A: flucloxacillin 1 g IV immediately prior to implant procedure and 500 mg orally every 6 h for 48 h post procedure (constituted 89% of Group A patients). Those allergic to penicillin received clindamycin 600 mg IV prior to implant procedure followed by 300 mg orally every 6 h for 48 h post procedure (constituted 11% of Group A patients) (n = 224). Group B: no antibiotic prophylaxis (n = 249). Both groups: skin prepared at time of operation with 10% povidone iodine solution or 0.5% alcoholic chlorhexidine.
Outcomes	Incidence of infection classified as: repeat operation for an infective complication (septicaemia, pocket abscess, or erosion of generator through the skin); patients with superficial wound infections that required only local treatment or antibiotics by mouth were not deemed to be infected.
Notes	Disclosures not noted. Adverse reactions intervention were not noted. We assumed that as systemic IV antibiotic prophylaxis was administered immediately prior to the procedure, that this fell within the hour prior window. Timing of initial perioperative systemic antibiotic administration unclear - study stated immediately before. The following were also noted: Group A: corticosteroid use (n = 19); repeat operation, non-infective complication (n = 4); Group B: corticosteroid use (n = 14); repeat operation, non-infective complication (n = 4).

Risk of bias table

Item	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear	Not stated - study was stated to be "randomised" but did not report the method of sequence generation.
Allocation concealment?	Unclear	Study did not mention whether allocation to the particular intervention group was concealed just prior to administering it.
Blinding? All outcomes - patients	Unclear	Study did not mention whether patients were blinded to the intervention.
Blinding? All outcomes - intervention providers	Unclear	Study did not mention whether physicians administering the antibiotic prophylaxis were blinded to the intervention given.
Blinding? All outcomes - outcome assessors	Unclear	Study did not mention whether physicians evaluating patients for the presence or absence of an infection were blinded to the intervention given.
Incomplete outcome data addressed?	Yes	Patients excluded from randomisation were noted.
Free of selective reporting?	Yes	Stated in trial under results section that: *" Non-randomized patients who received antibiotic prophylaxis were included in the analysis of predictors of pacemaker infection."*
Free of other bias?	Unclear	Other risks of bias were not noted in the trial.

Dwivedi 2001

Methods	RCT; randomisation scheme unclear; single-centre trial; country of origin: India. Allocation concealment: unclear. Blinding: unclear. ITT: unclear. A priori power calculation: unclear. Reliable primary outcome: yes. Length of follow-up (SD): Group A: mean 9.3 (1.8) months (range 1-17.3 month); Group B: mean 8.9 (2.0) months (range 1-16.5 month).
Participants	Consecutive male and female participants admitted for 1st time pacemaker implantation. Unclear whether informed consent obtained. Average age (SD): Group A - 46 (20.4) years; Group B - 45.4 (19.9) years Trial exclusion criteria: patients with diabetes; renal failure; hepatic failure; malignancy; corticosteroid treatment; revision pacemaker; pacemaker lead revision. Total pacemaker implant participants randomised to trial = 178.
Interventions	Group A: (PSA) 2 g IV cloxacillin 2 h prior to surgery. Ampicillin and cloxacillin (50 mg/kg/day divided into 4 doses), and gentamycin (3 mg/kg/day in 2 divided doses) for 2 days plus local antiseptic: Savlon, ether, and iodine (n = 88). Group B: (PSA) 2 g IV cloxacillin 2 h prior to surgery. Ampicillin and cloxacillin (50 mg/kg/day divided into 4 doses), and gentamycin (3 mg/kg/day in 2 divided doses) for 7 days plus local antiseptic: Savlon, ether, iodine (n = 90).
Outcomes	Incidence of infection was defined as follows: repeat operation due to acute local inflammation with an oral temperature >37.5 ^{o}C after day 4 postoperatively in absence of any other cause of fever, with or without pus in the generator pocket during hospitalisation.
Notes	No disclosures noted. No adverse events noted; no allergic reactions to prophylactic antibiotics noted. No mention of pacemaker placement, however, it was assumed that all pacemakers were placed in the pectoral region due to the date of publication. Temporary pacing wires: 131 patients in Groups A and B received a temporary pacing wire - but not clear how many in each group - either through the femoral (n = 90), or the subclavian (n = 41) route. 21 in Group A, 16 in Group B received IV injections of ampicillin and cloxacillin (500 mg qid) and gentamicin (60 mg bid) for 1-8 days prior to surgery, and 94 received 2 injections of ampicillin with cloxacillin (500 mg each) and gentamicin (80 mg), 1 participant prior to insertion of the temporary pacemaker wire, and the other 93, 6 h afterwards. The pacemaker was implanted after a mean of 4.1 (2.6) days.

Risk of bias table

Item	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear	Not stated - study was stated to be "randomised" but did not report the method of sequence generation.
Allocation concealment?	Unclear	Study did not mention whether allocation to the particular intervention group was concealed just prior to administering it.
Blinding? All outcomes - patients	Unclear	Study did not mention whether patients were blinded to the intervention.
Blinding? All outcomes - intervention providers	Unclear	Study did not mention whether physicians administering the antibiotic prophylaxis were blinded to the intervention given.
Blinding? All outcomes - outcome assessors	Unclear	Study did not mention whether physicians evaluating patients for the presence or absence of an infection were blinded to the intervention given.
Incomplete outcome data addressed?	Yes	All data appeared to be accounted for.
Free of selective reporting?	Yes	All patients in study accounted for in analysis along with results of primary outcome.
Free of other bias?	Unclear	Other risks of bias were not noted in the trial.

Chaudhry 2005

Methods	RCT; randomisation scheme unclear, single-centre trial; country of origin USA. According to communication with author: 2 catheterization laboratories in the same centre used in the trial. In 1 patients were randomised to "infiltration/local" (intervention), and to "no infiltration" in the other. Allocation concealment: unclear. According to communication with author re blinding: patients were blinded to the treatment, though treating physicians, and cardiologists evaluating patients in follow-up were not. ITT: unclear, however, it appears from the reporting of results that all patients randomised were followed-up. Power calculation: unclear. Reliable primary outcome: yes. Length of follow-up: 30 months. Patients were followed up at 1 and 6 months for evaluation of infection.
Participants	Ratio of male to female participants and other baseline characteristics unclear. Lead author of trial no longer has access to this information. Patients either received a new pacemaker implant or a replacement. Implants in pectoral region. Trial exclusion criteria (according to communication with author): ICD implants, CRT implants, and generator changes; taking antibiotics for existing conditions. Total pacemaker implant participants randomised to trial = 393. Group A = 176 (new pacemaker implant), 39 (generator replacement); Group B = 151 (new pacemaker implant), 27 (generator replacement).
Interventions	Group A: betadine solution; plus PSA (IV cefazolin preoperatively + 2 doses postoperatively) + local antiseptic, followed by 5 days of oral cephalexin (n = 215). Note: Cefazolin was administered in the following dosages: 1 g q8 hourly X 3 doses with the first dose administered within one hour prior to the procedure. Group B: PSA (IV 1 g cefazolin preoperatively + 2 doses postoperatively, or 1 g vancomycin both within 1 h prior to procedure) plus local antiseptic. This was followed by 5 days of oral cephalexin (n = 178). For patients with allergies, 1 dose of vancomycin IV preoperatively was followed by 5 days of clindamycin, but numbers that required this are unclear. As noted above in methods section: infiltration vs. no infiltration refers to local antibiotic/antiseptic administration perioperatively. The infiltration consisted of either betadine or vancomycin flush. Unfortunately, there was no data available as to which patients received betadine or vancomycin flush (also see notes below).
Outcomes	According to communications with author: Incidence of infection in pacemaker pocket: local signs of erythema, swelling, tenderness, warmth to touch or oozing. Systemic signs of infection included: fever, chills, leucocytosis of bacteraemia. Lastly, any use of antibiotics beyond 5 days for any concerns regarding the wound was considered an infectious event.
Notes	No disclosures noted. No adverse effects to antibiotics noted for Group A (antibiotic infiltration). Other interventions given to patients included IV antibiotics followed by oral antibiotics for 5 days. Timing of initial perioperative administration of systemic antibiotics unclear. Group A received either betadine or vancomycin infiltration - numbers in each group unclear, and which of these patients (by infiltration type) had an infection (total of 2 in this group). Two patients with an infection in Group A were diabetic and 1 in Group B with an infection was diabetic. Methodological quality of study: poor. Via communications with author (Chaudhry) in early 2010, it was noted that ≈90% of the infiltration group (or "local antibiotic") received betadine infiltration (20 ml) with ≈10% receiving antibiotic infiltration. The comparison of systemic IV antibiotic plus local infiltration vs systemic antibiotic was made on this basis.

Risk of bias table

Item	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear	Not stated - study was stated to be "randomised" but did not report the method of sequence generation - communications with author could not clarify this.
Allocation concealment?	Unclear	Study did not mention whether allocation to the particular intervention group was concealed just prior to administering it - communications with author could not clarify this.
Blinding? All outcomes - patients	Yes	Patients were blinded to treatment according to communications with author.
Blinding? All outcomes - intervention providers	No	Physicians administering pocket infiltration were not blinded to treatment - according to communications with author.
Blinding? All outcomes - outcome assessors	No	Clinician assessing outcomes was not blinded to intervention - according to communications with author.
Incomplete outcome data addressed?	Yes	According to author, all patients enrolled were followed-up at 1 and 6 months.
Free of selective reporting?	Unclear	Not stated in study, as results were in abstract form only - this could not be clarified by communication with author.
Free of other bias?	Unclear	Not stated in study as results were in abstract form only - this could not be clarified by communication with author.

Morito 2006

Methods	RCT; randomisation scheme unclear; single-centre trial; country of origin: Japan. Allocation concealment: unclear. Blinding: unclear. ITT: unclear, however, all patients randomised appeared to have been followed-up. Power calculation: unclear. Reliable primary outcome: yes. Length of follow-up: 7 days.
Participants	Male and female participants admitted for pacemaker implant or pacemaker generator replacement due to battery depletion. Pacemakers implanted over the pectoral major muscle. Consent for participation in trial unclear. Average age (SD): Group A = 75.7 (9.3) years; Group B = 73.7 (14.4) years. Trial exclusion criteria: none noted. Total pacemaker implant patients randomised to trial = 39.
Interventions	Group A: IV administration of 2 g cefazolin daily for 5 days postoperatively (n = 19). Group B: oral administration levofloxacin (LVFX) both pre- and postoperatively. Dose of LVFX varied based on renal function of patient. LVFX administered 2 h preoperatively, then for 5 days postoperatively. Patients with normal renal function and a CCr > 70 ml/min received 200 mg LVFX 2 h preoperatively and 400 mg/day for 5 days postoperatively. Patients with CCr 40-70 ml/min received 100 mg LVFX 2 h preoperatively and 200 mg/day for 5 days postoperatively. Patients with CCr 20-40 ml/min received 100 mg LVFX 2 h preoperatively and 100 mg/day for 5 days postoperatively. Finally, patients with CCr < 20 ml/min received 100 mg LVFX 2 h preoperatively and 100 mg/day for 3 days postoperatively (n = 20).
Outcomes	Incidence of infection at up to 7 days postoperatively. Infection defined as: inflammation (i.e. body temperature, blood C-reactive protein, and white blood cell concentration) evaluated before surgery, and 1, 4, and 7 days after surgery.
Notes	No disclosures noted. Adverse events to intervention not noted. Attempted to contact author about several methodological issues.

Risk of bias table

Item	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear	Not stated - study was stated to be "randomised" but did not report the method of sequence generation.
Allocation concealment?	Unclear	Study did not mention whether allocation to the particular intervention group was concealed just prior to administering it.
Blinding? All outcomes - patients	Unclear	Study did not mention whether patients were blinded to the intervention.
Blinding? All outcomes - intervention providers	Unclear	Study did not mention whether physicians administering the antibiotic prophylaxis were blinded to the intervention given.
Blinding? All outcomes - outcome assessors	Unclear	Study did not mention whether physicians evaluating patients for the presence or absence of an infection were blinded to the intervention given.
Incomplete outcome data addressed?	Yes	On the basis of the study results, all data appear to have been collected.
Free of selective reporting?	Yes	On the basis of the study results, all data appear to have been collected.
Free of other bias?	Yes	Other risks of bias were not noted in the trial.

De Oliveira 2009

Methods	RCT; randomisation scheme unclear; multicentred trial; country of origin: Brazil. Allocation concealment: unclear. Blinding: double-blinded study, however, unclear which provider was blinded - the anaesthesiologist (administering treatment) or the attending surgeon (implanting pacemaker), or both. ITT: no. Patients in the study who had a 2nd procedure for lead revision, or replacement due to lead dislodgement, within a 6 month follow-up period were subsequently excluded from the trial and not analysed under ITT. Power calculation: yes; 90% power to detect a 2% difference (assuming alpha error of 5%). Reliable primary outcome: yes. Length of follow-up: 6 months.
Participants	Male and female participants admitted for pacemaker implant procedure (generator plus lead) as inpatients, or generator change as outpatients. Implant type as follows: pacemaker (n = 591); ICD (n = 50); and cardiac resynchronisation therapy (CRT) (n = 8). Consent obtained for those enrolled in trial. Average age (SD) = 64 (15) years. Trial exclusion criteria: already taking antibiotics; patients in remote locations that precluded follow-up; those < 18 years undergoing thoracotomy; any surgery in previous 30 days; infection in previous 30 days; high risk patients, i.e. those with mechanical heart valves; requiring repeat procedures for lead revision; allergy to penicillin. Total pacemaker implant participants randomised in trial = 649.
Interventions	Group A: IV cefazolin 1 g immediately prior to surgery; dose not adjusted for patient weight (n = 314). Group B: IV saline immediately prior to surgery (n = 335). Both groups: at time of procedure, local antiseptic (10% povidone iodine and 0.5% alcohol chlorhexidine) used at surgical site.
Outcomes	Incidence of infection at 6 month follow-up. Infection classified as: superficial infections characterised by local inflammation (swelling, warmth, erythema) and pus; pocket infection without systemic manifestation; purulent discharge with positive culture from surgical wound site along with at least 2 of: pain, warmth, erythema, or local fluctuance. Systemic infection defined as pocket infection along with at least 2 of: fever, (> 38 ^{o}C), or hypothermia (< 36 ^{o}C), tachycardia (> 90 bpm), tachypnoea (> 20 respirations/minute), leukocytosis (> 12,000 cell/mm) or leukopenia (< 4,000 cells/mm).
Notes	No disclosures. The only adverse event noted was mortality; allergic reactions to cefazolin not noted. There were 15 deaths in the entire study population (6 deaths in the cefazolin group & 9 deaths in the saline/placebo group) during the follow up period. None of these deaths were caused by the infection or directly related to the procedure involving the implantation of the device. Attempted to contact main author twice via email regarding additional information concerning allocation concealment, randomisation scheme, and blinding, but without success.

Risk of bias table

Item	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear	Not stated - study was stated to be "randomised" but did not report the method of sequence generation.
Allocation concealment?	Unclear	Study did not mention whether allocation to the particular intervention group was concealed just prior to administering it.
Blinding? All outcomes - patients	Yes	Assumption was that participants were blinded, as study stated it was double-blinded.
Blinding? All outcomes - intervention providers	Yes	Yes - study stated that intervention was double-blinded, however, it was not clear which provider was blinded - anaesthesiologist administering antibiotic or surgeon performing implant procedure. Methods section states: *"This was a double-blinded study'*.
Blinding? All outcomes - outcome assessors	Unclear	Unclear whether clinician assessing outcomes was blinded to intervention. This was not stated in the study.
Incomplete outcome data addressed?	No	Yes - patients who underwent a 2nd procedure for lead revision/replacement due to lead dislodgement within a 6 month follow-up period were subsequently excluded from the trial and not analysed under ITT.
Free of selective reporting?	No	Patients who underwent a 2nd procedure for lead revision/replacement due to lead dislodgement within a 6 month follow-up period were subsequently excluded from trial and not analysed under ITT.
Free of other bias?	Unclear	Other risks of bias were not noted in the trial.

Dwivedi 2009

Methods	RCT; randomisation scheme unclear; single-centre trial; country of origin: India. Allocation concealment: unclear. Blinding: unclear. ITT: unclear, however, it seems that all the patients were enrolled and analysed. Power calculation: unclear. Reliable primary outcome: yes. Length of follow-up: unclear.
Participants	Male and female participants admitted for primary pacemaker implant (pacemaker plus lead), or generator replacement. Unclear what portion of implants were primary and what proportion replacements. Implant in pectoral region. Unclear whether informed consent given. Average age = 63.6 years. Trial exclusion criteria: not stated. Total pacemaker implant patients randomised to trial = 252.
Interventions	Group A: (PSA) IV teicoplanin 400 mg 2 h prior to procedure and at 24 h, and 2 ml (80 mg) gentamicin solution irrigation just prior to closure of incision (n = 133). Group B: (PSA) IV teicoplanin 400 mg 2 h prior to procedure and at 24 h, and 2 ml (80 mg) normal saline solution irrigation just prior to closure of incision (n = 119).
Outcomes	Incidence of pacemaker pocket infection: infection defined as fever beyond 48 h of implant and any 1 of: local redness around wound site; swelling, tenderness and pus discharge; or late pus discharge when fluctuant swelling (abscess); or device extrusion noted with, or without, fever requiring pacemaker revision.
Notes	No disclosures noted.

Risk of bias table

Item	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear	Not stated - study was stated to be "randomised" but did not report the method of sequence generation.
Allocation concealment?	Unclear	Study did not mention whether allocation to the particular intervention group was concealed just prior to administering it.
Blinding? All outcomes - patients	Unclear	Study did not mention whether patients were blinded to the intervention.
Blinding? All outcomes - intervention providers	Yes	Physician administering irrigation solution to pacemaker pocket was blinded.
Blinding? All outcomes - outcome assessors	Unclear	Unclear whether clinician assessing outcomes was blinded to intervention. This was not stated in the study.
Incomplete outcome data addressed?	Yes	Based on study results, all data appear to have been collected.
Free of selective reporting?	Yes	Based on study results, all data appear to have been collected.
Free of other bias?	Yes	Other risks of bias were not noted in the trial.

Footnotes

Abbreviations

> = greater/more than
< = less than

≈ = approximately equal to
bid = twice a day
bpm = beats per minute
CCr = creatine clearance
CRMD =cardiac rhythm management device
CRT = cardiac resynchronization therapy
h = hour(s)
ICD = implantable cardioverter defibrillator
ITT = intention-to-treat analysis
IV = intravenous(ly)
LVFX = levofloxacin
mm = millimetre
NS =not significant
PIVA = perioperative IV antibiotics

PSA - perioperative systemic antibiotic(s)
qid = four times a day
QRCT = Quasi-randomized controlled trial
RCT = randomised controlled trial
SD = standard deviation
tid = three times a day
vs = versus

Characteristics of excluded studies

Muers 1981

Reason for exclusion	Quasi-RCT; allocation according to last digit of hospital record number: odd numbers received treatment; even numbers did not.

Footnotes

Characteristics of studies awaiting classification

Footnotes

Characteristics of ongoing studies

Footnotes

Summary of findings tables

Additional tables

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Other published versions of this review

Classification pending references

Data and analyses

1 Perioperative IV antibiotics (PIVA) compared with no antibiotics

Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate
1.1 Incidence of infection	6	1766	Risk Ratio (M-H , Random , 95% CI)	0.13 [0.05, 0.36]
1.2 Adverse events	1	100	Risk Ratio (M-H , Random , 95% CI)	7.00 [0.37, 132.10]
1.3 Incidence of infection: new vs replacement implants	2	364	Risk Ratio (M-H , Random , 95% CI)	1.55 [0.09, 25.35]

2 PIVA plus local antiseptic wound infiltration compared with PIVA

Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate
2.1 Incidence of infection	1	393	Risk Ratio (M-H , Random , 95% CI)	1.66 [0.15, 18.11]

3 PIVA compared intraoperative local antibiotics

Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate
3.1 Incidence of infection	2	177	Risk Ratio (M-H , Random , 95% CI)	0.45 [0.10, 2.03]

4 PIVA plus local intraoperative antibiotics compared with local intraoperative antibiotics

Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate
4.1 Incidence of infection	1	500	Risk Ratio (M-H , Random , 95% CI)	0.65 [0.27, 1.53]
4.2 Adverse events	1	500	Risk Ratio (M-H , Random , 95% CI)	11.54 [0.64, 207.57]

5 PIVA plus local intraoperative antibiotics compared with PIVA

Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate
5.1 Incidence of infection	1	252	Risk Ratio (M-H , Random , 95% CI)	1.34 [0.39, 4.64]

6 Comparisons between alternative antibiotics

Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate
6.1 Incidence of infection	1	38	Risk Ratio (M-H , Random , 95% CI)	0.73 [0.05, 10.78]

7 Duration of antibiotic prophylaxis administration

Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate
7.1 Incidence of infection - 2 day vs. 7 day antibiotic	1	170	Risk Ratio (M-H , Random , 95% CI)	0.75 [0.13, 4.38]
7.2 Incidence of infection: perioperative vs peri-postoperative antibiotic	1	505	Risk Ratio (M-H , Random , 95% CI)	Not estimable

8 Comparison between different antibiotic regimens: route of administration

Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate
8.1 Incidence of infection	1	39	Risk Ratio (M-H , Random , 95% CI)	Not estimable

10 Timing of antibiotic administration

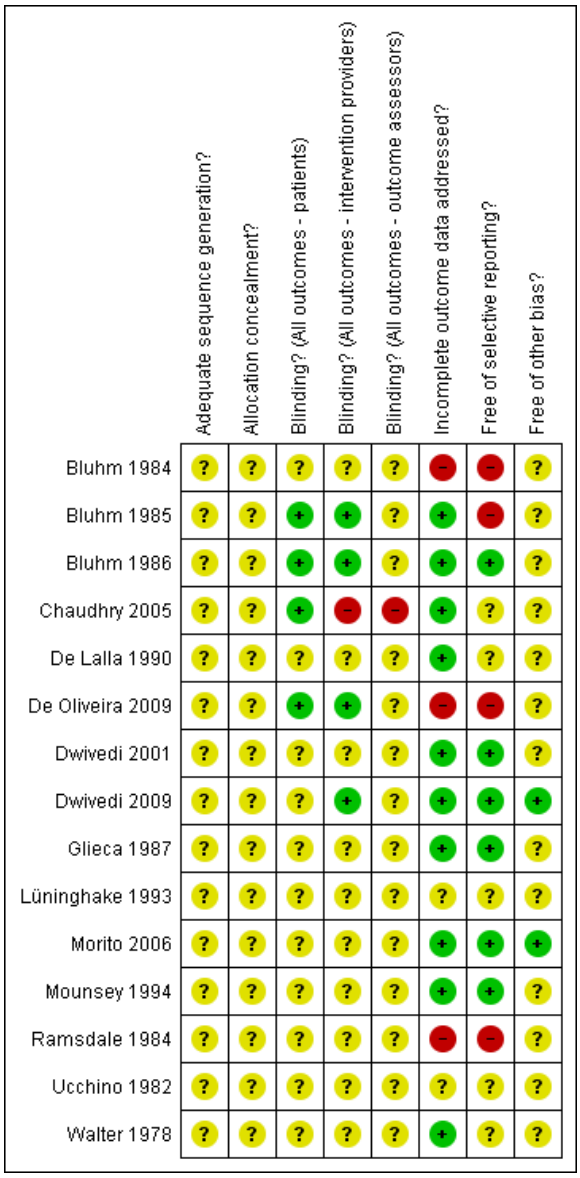
Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate
10.1 Incidence of infection	1	100	Risk Ratio (M-H , Random , 95% CI)	0.14 [0.03, 0.60]

11 Perioperative antibacterial agent compared with local antiseptic

Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate
11.1 Incidence of infection	1	166	Risk Ratio (M-H , Random , 95% CI)	0.58 [0.02, 14.13]

Figures

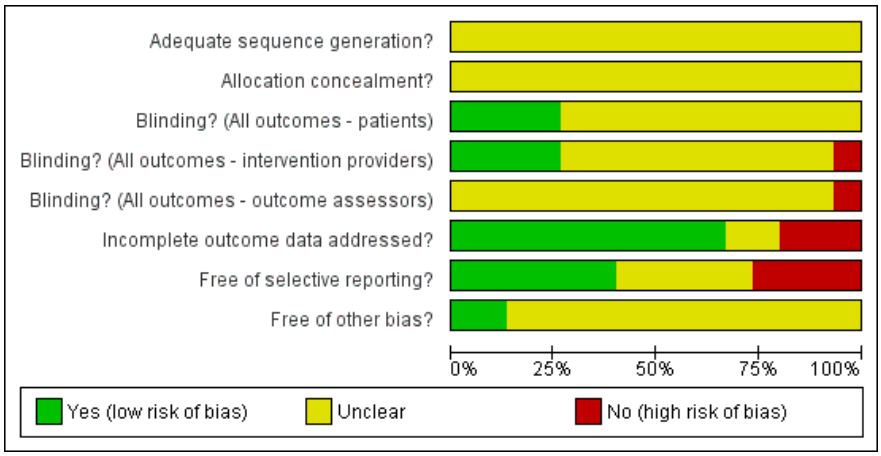
Figure 1



Caption

Methodological quality summary: review authors' judgements about each methodological quality item for each included study.

Figure 2



Caption

Methodological quality graph: review authors' judgements about each methodological quality item presented as percentages across all included studies.

Sources of support

Internal sources

- No sources of support provided

External sources

- NIHR/Department of Health (England), Cochrane Wounds Group, UK

Feedback

Appendices

1 Ovid MEDLINE search strategy

1 exp Anti-Bacterial Agents/
2 exp Vancomycin/
3 exp Cephalosporins/
4 exp Ciprofloxacin/
5 exp Ofloxacin/
6 exp Aztreonam/
7 exp Trimethoprim-Sulfamethoxazole Combination/
8 exp Oxazolidinones/
9 (antibiotic* or antibacterial* or antimicrobial* or cefazolin or cefepime or vancomycin or aztreonam or ciprofloxacin or levaquin or trimethoprim or linezolid).tw.
10 exp Anti-Infective Agents, Local/
11 antiseptic*.tw.
12 exp Iodophors/
13 exp Chlorhexidine/
14 exp Povidone-Iodine/
15 exp Alcohols/
16 (iodophor* or povidone or iodine or chlorhexidine or betadine or alcohol*).tw.
17 or/1-16
18 exp Surgical Wound Infection/
19 exp Surgical Wound Dehiscence/
20 (surgical adj5 infection*).tw.
21 (surgical adj5 wound*).tw.
22 (surg* adj5 site*).tw.
23 (surg* adj5 incision*).tw.
24 ((post-operative or postoperative) adj wound infection*).tw.
25 or/18-24
26 exp Pacemaker, Artificial/
27 exp Defibrillators, Implantable/
28 exp Cardiac Pacing, Artificial/
29 (pacemaker* or cardioverter defibrillator* or (implantable adj3 defibrillator*)).tw.
30 (cardiac rhythm management device* or CRMD*).tw.
31 or/26-30
32 17 and 25 and 31

2 Ovid EMBASE search strategy

1 exp Antibiotic Agent/
2 exp Vancomycin/
3 exp Cephalosporin Derivative/
4 exp Ciprofloxacin/
5 exp Ofloxacin/
6 exp Aztreonam/
7 exp Cotrimoxazole/
8 exp Oxazolidinone Derivative/
9 (antibiotic* or antibacterial* or antimicrobial* or cefazolin or cefepime or vancomycin or aztreonam or ciprofloxacin or levaquin or trimethoprim or linezolid).tw.
10 exp Topical Antiinfective Agent/
11 antiseptic*.tw.
12 exp Iodophor/
13 exp Chlorhexidine/
14 exp Povidone Iodine/
15 exp Alcohol Derivative/
16 (iodophor* or povidone or iodine or chlorhexidine or betadine or alcohol*).tw.
17 or/1-16
18 exp Surgical Infection/
19 exp Wound Dehiscence/
20 (surgical adj5 infection*).tw.
21 (surgical adj5 wound*).tw.
22 (surg* adj5 site*).tw.
23 (surg* adj5 incision*).tw.
24 ((post-operative or postoperative) adj wound infection*).tw.
25 or/18-24
26 exp Artificial Heart Pacemaker/
27 exp Defibrillator/
28 Heart Pacing/
29 (pacemaker* or cardioverter defibrillator* or (implantable adj3 defibrillator*)).tw.
30 (cardiac rhythm management device* or CRMD*).tw.
31 or/26-30
32 17 and 25 and 31

3 EBSCO CINAHL search strategy

S32 S17 and S25 and S31
S31 S26 or S27 or S28 or S29 or S30
S30 TI (cardiac rhythm management device* or CRMD*) or AB (cardiac rhythm management device* or CRMD*)
S29 TI (pacemaker* or cardioverter defibrillator* or implantable N3 defibrillator*) or AB (pacemaker* or cardioverter defibrillator* or implantable N3 defibrillator*)
S28 (MH "Cardiac Pacing, Artificial")
S27 (MH "Defibrillators, Implantable")
S26 (MH "Pacemaker, Artificial")
S25 S18 or S19 or S20 or S21 or S22 or S23 or S24
S24 TI (post-operative wound infection* or postoperative wound infection*) or AB (post-operative wound infection* or postoperative wound infection*)
S23 TI surgical N5 incision* or AB surgical N5 incision*
S22 TI surgical N5 site* or AB surgical N5 site*
S21 TI surgical N5 wound* or AB surgical N5 wound*
S20 TI surgical N5 infection* or AB surgical N5 infection*
S19 (MH "Surgical Wound Dehiscence")
S18 (MH "Surgical Wound Infection")
S17 S1 or S2 or S3 or S4 or S5 or S6 or S7 or S8 or S9 or S10 or S11 or S12 or S13 or S14 or S15 or S16
S16 TI (iodophor* or povidone or iodine or chlorhexidine or betadine or alcohol*) or AB (iodophor* or povidone or iodine or chlorhexidine or betadine or alcohol*)
S15 (MH "Alcohols+")
S14 (MH "Iodine Compounds")
S13 (MH "Povidone-Iodine")
S12 (MH "Chlorhexidine")
S11 TI antiseptic* or AB antiseptic*
S10 (MH "Antiinfective Agents, Local+")
S9 TI (antibiotic* or antibacterial* or antimicrobial* or cefazolin or cefepime or vancomycin or aztreonam or ciprofloxacin or levaquin or trimethoprim or linezolid) or AB (antibiotic* or antibacterial* or antimicrobial* or cefazolin or cefepime or vancomycin or aztreonam or ciprofloxacin or levaquin or trimethoprim or linezolid)
S8 Oxazolidinones
S7 (MH "Trimethoprim-Sulfamethoxazole Combination")

S6 (MH "Aztreonam")
S5 (MH "Ofloxacin")
S4 (MH "Ciprofloxacin")
S3 (MH "Cephalosporins+")
S2 (MH "Vancomycin")
S1 (MH "Antibiotics+")

4 Criteria for assessment of risk of bias

1. Was the allocation sequence randomly generated?

Low risk of bias

The investigators describe a random component in the sequence generation process such as: referring to a random number table; using a computer random number generator; coin tossing; shuffling cards or envelopes; throwing dice; drawing of lots.

High risk of bias

The investigators describe a non-random component in the sequence generation process. Usually, the description would involve some systematic, non-random approach, for example: sequence generated by odd or even date of birth; sequence generated by some rule based on date (or day) of admission; sequence generated by some rule based on hospital or clinic record number.

Unclear

Insufficient information about the sequence generation process to permit judgement of low or high risk of bias.

2. Was the treatment allocation adequately concealed?

Low risk of bias

Participants and investigators enrolling participants could not foresee assignment because one of the following, or an equivalent method, was used to conceal allocation: central allocation (including telephone, web-based and pharmacy-controlled randomisation); sequentially-numbered drug containers of identical appearance; sequentially-numbered, opaque, sealed envelopes.

High risk of bias

Participants or investigators enrolling participants could possibly foresee assignments and thus introduce selection bias, such as allocation based on: using an open random allocation schedule (e.g. a list of random numbers); assignment envelopes were used without appropriate safeguards (e.g. if envelopes were unsealed or non- opaque or not sequentially numbered); alternation or rotation; date of birth; case record number; any other explicitly unconcealed procedure.

Unclear

Insufficient information to permit judgement of low or high risk of bias. This is usually the case if the method of concealment is not described or not described in sufficient detail to allow a definite judgement, for example if the use of assignment envelopes is described, but it remains unclear whether envelopes were sequentially numbered, opaque and sealed.

3. Blinding - was knowledge of the allocated interventions adequately prevented during the study?

Low risk of bias

Any one of the following.

- No blinding, but the review authors judge that the outcome and the outcome measurement are not likely to be influenced by lack of blinding.
- Blinding of participants and key study personnel ensured, and unlikely that the blinding could have been broken.
- Either participants or some key study personnel were not blinded, but outcome assessment was blinded and the non-blinding of others unlikely to introduce bias.

High risk of bias

Any one of the following.

- No blinding or incomplete blinding, and the outcome or outcome measurement is likely to be influenced by lack of blinding.
- Blinding of key study participants and personnel attempted, but likely that the blinding could have been broken.
- Either participants or some key study personnel were not blinded, and the non-blinding of others likely to introduce bias.

Unclear

Any one of the following.

- Insufficient information to permit judgement of low or high risk of bias.
- The study did not address this outcome.

4. Were incomplete outcome data adequately addressed?

Low risk of bias

Any one of the following.

- No missing outcome data.
- Reasons for missing outcome data unlikely to be related to true outcome (for survival data, censoring unlikely to be

introducing bias).
- Missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across groups.
- For dichotomous outcome data, the proportion of missing outcomes compared with observed event risk not enough to have a clinically relevant impact on the intervention effect estimate.
- For continuous outcome data, plausible effect size (difference in means or standardised difference in means) among missing outcomes not enough to have a clinically relevant impact on observed effect size.
- Missing data have been imputed using appropriate methods.

High risk of bias

Any one of the following.

- Reason for missing outcome data likely to be related to true outcome, with either imbalance in numbers or reasons for missing data across intervention groups.
- For dichotomous outcome data, the proportion of missing outcomes compared with observed event risk enough to induce clinically relevant bias in intervention effect estimate.
- For continuous outcome data, plausible effect size (difference in means or standardized difference in means) among missing outcomes enough to induce clinically relevant bias in observed effect size.
- 'As-treated' analysis done with substantial departure of the intervention received from that assigned at randomisation.
- Potentially inappropriate application of simple imputation.

Unclear

Any one of the following.

- Insufficient reporting of attrition/exclusions to permit judgement of low or high risk of bias (e.g. number randomized not stated, no reasons for missing data provided).
- The study did not address this outcome.

5. Are reports of the study free of suggestion of selective outcome reporting?

Low risk of bias

Any of the following.

- The study protocol is available and all of the study's pre-specified (primary and secondary) outcomes that are of interest in the review have been reported in the pre-specified way.
- The study protocol is not available but it is clear that the published reports include all expected outcomes, including those that were pre-specified (convincing text of this nature may be uncommon)

High risk of bias

Any one of the following.

- Not all of the study's pre-specified primary outcomes have been reported.
- One or more primary outcomes is reported using measurements, analysis methods or subsets of the data (e.g. subscales) that were not pre-specified.
- One or more reported primary outcomes were not pre-specified (unless clear justification for their reporting is provided, such as an unexpected adverse effect).
- One or more outcomes of interest in the review are reported incompletely so that they cannot be entered in a meta-analysis.
- The study report fails to include results for a key outcome that would be expected to have been reported for such a study.

Unclear

Insufficient information to permit judgement of low or high risk of bias. It is likely that the majority of studies will fall into this category.

6. Other sources of potential bias:

Low risk of bias

The study appears to be free of other sources of bias.

High risk of bias

There is at least one important risk of bias. For example, the study:

- had a potential source of bias related to the specific study design used; or
- had extreme baseline imbalance; or
- has been claimed to have been fraudulent; or
- had some other problem.

Unclear

There may be a risk of bias, but there is either:

- insufficient information to assess whether an important risk of bias exists; or
- insufficient rationale or evidence that an identified problem will introduce bias.

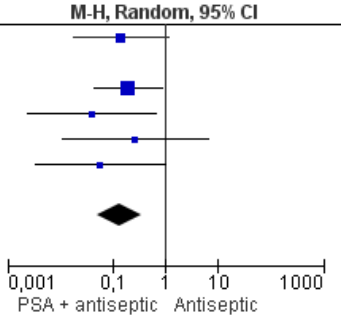
Graphs

1 - Perioperative IV antibiotics (PIVA) compared with no antibiotics

1.1 Incidence of infection

Study or Subgroup	PSA + antiseptic Events	Total	Antiseptic Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Bluhm 1984	1	50	7	50	22.9%	0.14 [0.02, 1.12]
Bluhm 1986	0	50	0	52		Not estimable
De Oliveira 2009	2	314	11	335	43.2%	0.19 [0.04, 0.87]
Glieca 1987	0	100	12	100	12.3%	0.04 [0.00, 0.67]
Lüninghake 1993	0	136	1	106	9.5%	0.26 [0.01, 6.33]
Mounsey 1994	0	224	9	249	12.1%	0.06 [0.00, 1.00]
Total (95% CI)		**874**		**892**	**100.0%**	**0.13 [0.05, 0.36]**
Total events	3		40			

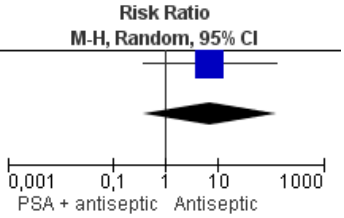
Heterogeneity: Tau² = 0.00; Chi² = 1.57, df = 4 (P = 0.81); I² = 0%
Test for overall effect: Z = 4.02 (P < 0.0001)



1.2 Adverse events

Study or Subgroup	PSA + antiseptic Events	Total	Antiseptic Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Bluhm 1984	3	50	0	50	100.0%	7.00 [0.37, 132.10]
Total (95% CI)		**50**		**50**	**100.0%**	**7.00 [0.37, 132.10]**
Total events	3		0			

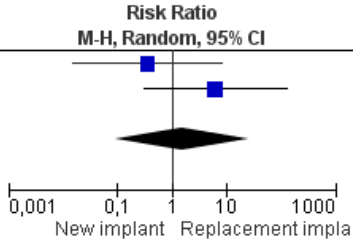
Heterogeneity: Not applicable
Test for overall effect: Z = 1.30 (P = 0.19)



1.3 Incidence of infection: new vs replacement implants

Study or Subgroup	New implant Events	Total	Replacement implant Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Bluhm 1984	0	24	1	26	48.8%	0.36 [0.02, 8.43]
De Oliveira 2009	2	140	0	174	51.2%	6.21 [0.30, 128.22]
Total (95% CI)		**164**		**200**	**100.0%**	**1.55 [0.09, 25.35]**
Total events	2		1			

Heterogeneity: Tau² = 1.58; Chi² = 1.64, df = 1 (P = 0.20); I² = 39%
Test for overall effect: Z = 0.31 (P = 0.76)

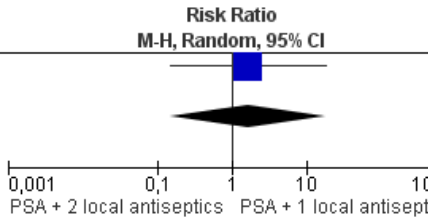


2 - PIVA plus local antiseptic wound infiltration compared with PIVA

2.1 Incidence of infection

Study or Subgroup	PSA + 2 local antiseptics Events	Total	PSA + 1 local antiseptic Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Chaudhry 2005	2	215	1	178	100.0%	1.66 [0.15, 18.11]
Total (95% CI)		**215**		**178**	**100.0%**	**1.66 [0.15, 18.11]**
Total events	2		1			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.41 (P = 0.68)

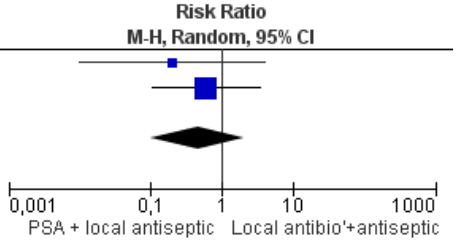


3 - PIVA compared intraoperative local antibiotics

3.1 Incidence of infection

Study or Subgroup	PSA + local antiseptic Events	Total	Local antibio'+ antisept' Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Bluhm 1985	0	53	2	52	24.8%	0.20 [0.01, 3.99]
Ucchino 1982	2	38	3	34	75.2%	0.60 [0.11, 3.36]
Total (95% CI)		**91**		**86**	**100.0%**	**0.45 [0.10, 2.03]**
Total events	2		5			

Heterogeneity: Tau² = 0.00; Chi² = 0.40, df = 1 (P = 0.53); I² = 0%
Test for overall effect: Z = 1.04 (P = 0.30)

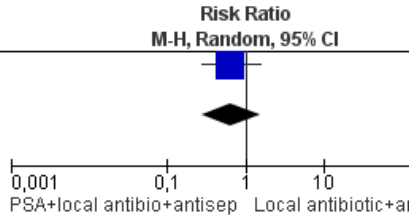


4 - PIVA plus local intraoperative antibiotics compared with local intraoperative antibiotics

4.1 Incidence of infection

Study or Subgroup	PSA+local antibio+antisep Events	Total	Local antibiotic+antisept Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Ramsdale 1984	8	244	13	256	100.0%	0.65 [0.27, 1.53]
Total (95% CI)		**244**		**256**	**100.0%**	**0.65 [0.27, 1.53]**
Total events	8		13			

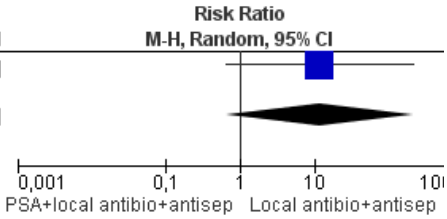
Heterogeneity: Not applicable
Test for overall effect: Z = 0.99 (P = 0.32)



4.2 Adverse events

Study or Subgroup	PSA+local antibio+antisep Events	Total	Local antibio+antisep Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Ramsdale 1984	5	244	0	256	100.0%	11.54 [0.64, 207.57]
Total (95% CI)		**244**		**256**	**100.0%**	**11.54 [0.64, 207.57]**
Total events	5		0			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.66 (P = 0.10)

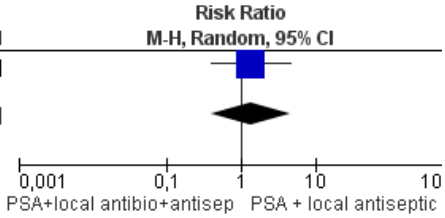


5 - PIVA plus local intraoperative antibiotics compared with PIVA

5.1 Incidence of infection

Study or Subgroup	PSA+local antibio+antisep Events	Total	PSA + local antiseptic Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Dwivedi 2009	6	133	4	119	100.0%	1.34 [0.39, 4.64]
Total (95% CI)		**133**		**119**	**100.0%**	**1.34 [0.39, 4.64]**
Total events	6		4			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.46 (P = 0.64)

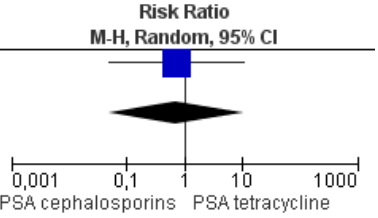


6 - Comparisons between alternative antibiotics

6.1 Incidence of infection

Study or Subgroup	PSA cephalosporins Events	Total	PSA tetracycline Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Ucchino 1982	1	22	1	16	100.0%	0.73 [0.05, 10.78]
Total (95% CI)		**22**		**16**	**100.0%**	**0.73 [0.05, 10.78]**
Total events	1		1			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.23 (P = 0.82)

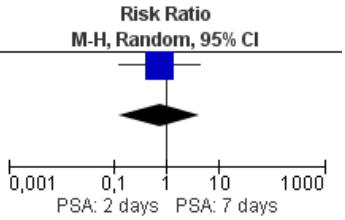


7 - Duration of antibiotic prophylaxis administration

7.1 Incidence of infection - 2 day vs. 7 day antibiotic

Study or Subgroup	PSA 2 days Events	Total	PSA 7 days Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Dwivedi 2001	2	80	3	90	100.0%	0.75 [0.13, 4.38]
Total (95% CI)		**80**		**90**	**100.0%**	**0.75 [0.13, 4.38]**
Total events	2		3			

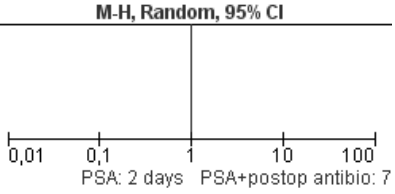
Heterogeneity: Not applicable
Test for overall effect: Z = 0.32 (P = 0.75)



7.2 Incidence of infection: perioperative vs peri-postoperative antibiotic

Study or Subgroup	PSA: 2 days Events	Total	PSA+postop antibio: 7days Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
De Lalla 1990	0	255	0	250		Not estimable
Total (95% CI)		**255**		**250**		**Not estimable**
Total events	0		0			

Heterogeneity: Not applicable
Test for overall effect: Not applicable

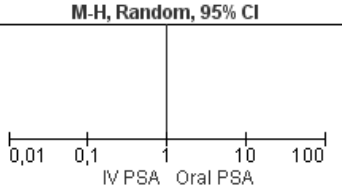


8 - Comparison between different antibiotic regimens: route of administration

8.1 Incidence of infection

Study or Subgroup	IV PSA Events	Total	Oral PSA Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Morito 2006	0	19	0	20		Not estimable
Total (95% CI)		**19**		**20**		**Not estimable**
Total events	0		0			

Heterogeneity: Not applicable
Test for overall effect: Not applicable

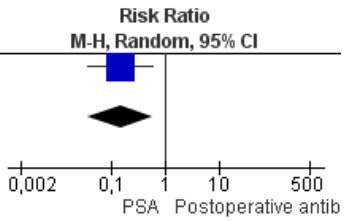


10 - Timing of antibiotic administration

10.1 Incidence of infection

Study or Subgroup	PSA Events	Total	Postoperative antibiotic Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Walter 1978	2	50	14	50	100.0%	0.14 [0.03, 0.60]
Total (95% CI)		**50**		**50**	**100.0%**	**0.14 [0.03, 0.60]**
Total events	2		14			

Heterogeneity: Not applicable
Test for overall effect: Z = 2.67 (P = 0.008)



11 - Perioperative antibacterial agent compared with local antiseptic

11.1 Incidence of infection

Study or Subgroup	Antibacterial+antiseptic Events	Total	Antiseptic Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Lüninghake 1993	0	60	1	106	100.0%	0.58 [0.02, 14.13]
Total (95% CI)		**60**		**106**	**100.0%**	**0.58 [0.02, 14.13]**
Total events	0		1			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.33 (P = 0.74)